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SYMPOSIUM ON
CLINICAL NEUROLOGY: NEW APPROACHES TO OLD PROBLEMS

William K. Hass, M.D., *Guest Editor*

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Symposium on Clinical Neurology: New Approaches to Old Problems

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Foreword

Most of us now contributing to the *Medical Clinics of North America* cut our medical eye-teeth on this journal. The once and future textbooks of medicine suffered and still suffer from publication lag times often in excess of three years. In contrast, the Medical Clinics were and clearly are *au courant.*

The occasional issue of past Medical Clinics devoted to Clinical Neurology contained articles which shaped the decision of many of the authors represented in this volume to enter the field of neurology. When many of us decided to become neurologists, our families put on the metaphorical garments of black and often inquired why we had given up general internal medicine for that "drab and hopeless specialty." The contents of this symposium testify to the fact that the ugly duckling, if not yet a swan, is well into a most satisfying metamorphosis.

The explosion in technology at both the basic science and the clinical levels has placed Neurology in the vanguard. Neurologists enjoy the frontier, taking pride in earlier conquests but delighting even more in uncovering further problems to solve. Angiography, first employed extensively for diagnosis, has helped to define the pathogenesis of ischemic cerebrovascular diseases to a degree no one thought imaginable a generation ago. Computed tomography (CT)—unknown at the time of the last issue of the Medical Clinics on Clinical Neurology—has found such widespread use that a basic knowledge of CT technology and diagnosis can now be assumed. We are now concerned with the delineation of pitfalls in CT interpretation and future applications of this technology to metabolic studies of the normal and diseased central nervous system. Advances in basic science similarly affect the described advances in the treatment of the cerebrovascular diseases, the dyskinesias, myasthenia gravis, and epilepsy.

We have prepared this issue motivated by feelings of sentiment, pride, and hopefulness. The reader, we trust, will share our feelings.

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The Pathophysiology of Transient Cerebral Ischemic Attacks

Therapy with Platelet Antiaggregants

*H. J. M. Barnett, M.D.**

Classical neurology concentrated on the description of the stroke syndromes produced by infarcts in the territory of the major intracranial arteries. Angiography redirected this focus and drew attention to the importance of the carotid and other arteries in the neck. Several series of meticulous pathological dissections[23, 35, 84] produced the anatomical corroboration of Moniz' pioneering radiological observations. As these new concepts about the cause of stroke unfolded, heparin and the coumarin derivatives were introduced as antithrombotic therapy. The availability of these agents encouraged surgeons to develop skill in arteriotomy and arterial repair. Transient neurological and ocular symptoms were identified as symptoms foreshadowing stroke. Serious studies aimed at preventing stroke now became mandatory.

Definitions

The common term to describe the forerunner of a stroke is *transient ischemic attack* (TIA). By convention, this is a neurological deficit of sudden onset interrupting the function of a portion of the brain or retina with rapid clearing after a period lasting for more than a few seconds and up to 24 hours. Ischemia extending beyond 24 hours, but not indefinitely, has been designated as a *reversible ischemic neurological deficit* (RIND). By contrast, the signs of stroke may persist. Such a permanent deficit may be partial (*partial nonprogressing stroke*, PNS), and remain so; may be partial and go on to further deficit (*progressing stroke*); or may be total and a *calamitous stroke* from the onset. Hard data are lacking as to the prognostic differences between patients with classical transient ischemic attack, with reversible ischemic neurological deficit, or with partial nonprogressing

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stroke, and this information is needed. For the time being, though, it is apparent that these three types of ischemia must be considered as potential candidates for worsening, all capable of developing into a total and devastating stroke.

PATHOGENESIS OF THE SYMPTOMS OF THREATENED STROKE

Rational stroke-prevention therapy is dependent upon an understanding of pathogenesis. Accordingly, this matter will be outlined herewith in some detail.

The early studies on the pathophysiology of transient ischemic attacks considered vasospasm and drop in systemic blood pressure as the likely mechanisms. Subsequent observations have led to the firm conviction that these ischemic events result, rather, from a variety of conditions, including hemodynamic factors, cardiac emboli, extracranial mechanical interference with arteries, altered coagulability, thrombocytosis, nonarteriosclerotic vasculopathies, lacunar infarction, and artery to artery emboli.

Hemodynamic Mechanisms

Early studies of cerebral blood flow supported the role of postural change. A 21 per cent reduction in cerebral blood flow occurred in 20 normal subjects raised from the supine position to an elevation of 65°.[66] A series of patients with symptomatic carotid and basilar disease was subjected to rapid tilting from supine to 70°.[52] The majority had recognizable electroencephalographic changes but symptoms developed in only 2 of the 23. A milestone study, however, demonstrated no reduction in carotid artery blood flow or pressure gradient change unless the stenosis of an internal carotid artery reduced the lumen below 5 mm. Furthermore, as long as the minimal lumen was 5 mm or more, the length of the stenosis was not significant. A series of stenoses or a long stenosis would reduce flow if maximal narrowing was to between 2 and 5 mm. Below 2 mm residual diameter, both the flow and the pressure gradient fell, regardless of the length of the stenosis.[11]

Thirty-seven subjects afflicted with transient ischemic attacks were submitted to a drug-induced reduction of blood pressure to a mean 42 per cent below their normal readings. Despite this radical change in hemodynamics, sufficient to render all subjects syncopal, transient ischemic attacks were reproduced in only 1 subject.[41] A series of patients who had survived for a period following cardiac arrest were studied at post mortem. Recent focal infarcts were *not* identified corresponding to existing atheroma in the cerebral arteries. However, old infarcts, preceding the fatal illness, correlated positively with the atheroma in these arteries. Unfortunately, the neck arteries were not examined exhaustively in all cases.[74]

To summarize, the early evidence in the study of extracranial arte-

rial disease tended to attribute the symptoms to posturally determined changes in blood flow. Then conflicting data appeared. Eventually, the weight of evidence has come to support hemodynamic mechanisms as important in a small number of cases of focal cerebral ischemia, but decidedly less often than was the early impression.

Perspective about the significance and importance of these hemodynamic disturbances to transient ischemic attack can be gained by considering briefly various circumstances in which a reduction of total cerebral blood flow may occur. Each entity should be considered in the light of particular preventive measures, since obviously, treatment will not be the same in many of the varieties. A few will be identified as potential candidates for antithrombotic therapy.

BRADYARRHYTHMIA-TACHYARRHYTHMIA. Focal cerebral ischemic events are negatively correlated with the occurrence of serious cardiac arrhythmias. In one large series of patients in whom pacemakers were inserted for bradyarrhythmia from heart block, the majority (239 of 290) had suffered neurological symptoms indicative of diffuse decrease in cerebral perfusion, with syncope as the most common. A mere 1.4 per cent experienced a focal transient ischemic attack.[63] Since atheroma in coronary arteries is the common cause of heart block, and is correlated convincingly with arteriosclerosis of the cerebral arteries, the failure of these patients to experience focal transient ischemic attacks carries special significance.[51]

ORTHOSTATIC SYSTEMIC HYPOTENSION. Whether produced by a fall in blood pressure related to drug therapy (antihypertensive drugs and antiparkinsonian drugs being the common offenders) or of spontaneous origin, orthostatic systemic hypotension leads uncommonly to focal neurological ischemic symptoms. Syncope, vertigo, nonspecific dizziness, blurred vision, and occasionally convulsions are the features that reflect this diffuse reduction in perfusion. Undoubtedly, there are exceptions. In a dramatic case of mid-basilar occlusion on record, excessive antihypertensive treatment produced sufficient orthostatic hypotension to render a patient bedridden. Florid focal brain stem signs recurred whenever he stood up, and no more than an adjustment in medication was required for their elimination.[3]

CAROTID SINUS HYPERSENSITIVITY. The common cause of carotid sinus hypersensitivity is atheromatous disease of the internal carotid artery. When this condition is productive of symptoms, they are in general, the result of, and comparable to, those of hypotension and bradyarrhythmia. When focal signs occur spontaneously or from manual stimulation, the suspicion must be strong that an embolus has been dislodged from the diseased intima of the carotid sinus.

ORTHOSTATIC TRANSIENT RETINAL AND CEREBRAL ISCHEMIA. Even without a measurable drop in systemic blood pressure, claims of orthostatic transient retinal and cerebral ischemia have been made in patients with major cerebral arterial occlusion and serious stenoses. Ophthalmodynamometric pressures, recorded in these patients recumbent and erect, showed lowered readings in association with focal symptoms.[73] Again without a systemic blood pressure drop,

worsening of symptoms has been related to the assumption of an erect position in a few patients afflicted with recent stroke.[14] It has been claimed that these observations indicate the failure of autoregulatory mechanisms in the jeopardized circulation. More definitive studies of this problem are needed. The possibility exists that intra-arterial readings rather than indirect blood pressure recordings would identify a significant orthostatic drop since thickened arterial walls may result in spuriously higher readings.[72]

Diffusely Impaired Cerebral Infusion. In the opinion of some writers, seriously stenosed and occluded major arteries result in a clinical picture of "diffusely impaired cerebral perfusion" with a capability of producing transient ischemic attacks. Undoubtedly, multiple major occlusions will result in some examples of intellectual impairment[9] but the prevalence of recurrent and fluctuating symptoms in these patients is low and their hemodynamic origin is ill defined. Knowledge in this area is sufficiently sketchy as to require cautious interpretation of the cause of symptoms in such cases.

Tight Aortic Stenosis and Failing Left Ventricle. These two mechanisms result in poor cerebral circulation related to exercise. A failing left ventricle may be accompanied by angina. At rest, no difficulty may be noted but with exertion, both conditions may result in diffuse, and only exceptionally focal, transient cerebral ischemic symptoms.

Vasospasm. Vasospasm in retina or brain sufficient to provoke transient ischemic attack does occur with migraine and subarachnoid hemorrhage. In their absence, a rare patient is encountered in whom recent very severe hypertension has developed and segmental retinal arteriolar narrowing can be recognized. The presumption may be made that a similar process, widespread in the cerebral arterioles, will induce transient ischemia. The distinction between this rare clinical entity and lacunar infarction is difficult and may be impossible. However, in the very seriously hypertensive patient, when retinal symptoms occur, alone or in company with other cerebral symptoms, vasospasm may be a reasonable consideration. This unusual variety of amaurosis will be featured, most probably, by concentric reduction of the visual field rather than the "window blind" or "gray wall" loss of the usual embolic variety.

Extracranial Arterial Steal. Diversion of blood in retrograde flow down a vertebral artery to supply a subclavian artery, the site of more proximal occlusion, has been a popular concept since its early description.[57] The "steal" phenomenon, with brain stem ischemia related to arm exercise, is very much less common than the angiographic demonstration of the hemodynamic diversion necessary for its identification. The symptomatic patients appear to be those in whom considerable obliterative disease also exists in the other main arteries to the brain. In the absence of extensive arterial disease; in the absence of a classical history; or in the presence of nonspecific symptoms alone (e.g., vertigo), the diagnosis should be approached very skeptically.

Cardiac Emboli

Embolic cerebral ischemic events from recent myocardial infarction and rheumatic mitral stenosis tend to result in calamitous strokes since the usual emboli are large. Nevertheless, these conditions, as well as a variety of more subtle abnormalities affecting the heart walls, chambers, and valves, are being recognized with increasing frequency as sites for transient and more persistent minor cerebral events. Cardiac imaging has become sufficiently sophisticated and available so that these sources of potential emboli deserve scrutiny in all cases of stroke and threatened stroke that are not readily recognizable as of arterial thrombotic origin. This is particularly true in the younger patient, but cannot be overlooked in patients of any age.

All cases of threatened stroke must be submitted to a careful cardiac history and a good examination of the heart. When doubt exists about the cause of the cerebral ischemic events, cardiac monitoring by 48 hour electrocardiogram studies and study by a variety of radiographic, radionuclide, and echocardiographic investigations may be indicated. Although myocardial infarction tends to be productive of emboli from mural thrombus within two months of the recent event, akinetic segments may be a source of thrombogenesis productive of emboli for indefinite periods thereafter. These can be detected by any or all of the methods mentioned above and representative examples are illustrated (Figs. 1 and 2).

Atrial myxoma, a rare but treatable condition, frequently declares itself by cerebral ischemic phenomena.[85] It is easily recognized by a variety of cardiac imaging techniques, the simplest of which is two-dimensional echocardiography. Bacterial endocarditis and nonbacterial thrombotic endocarditis may be evidenced for the first time by cerebral ischemic incidents. The diagnosis need not be discussed here but the need to consider them should be reiterated. The patient illustrated had a nonbacterial endocarditis with repeated transient ischemic attacks due to emboli (Figs. 3 and 4).

Recent years have led to the emergence of an awareness of the myxomatous degeneration of the mitral valve. Once thought benign, it is now known as a cause of progressive mitral regurgitation, as a predisposing factor for bacterial endocarditis; is known to have an association with cardiac arrhythmias including serious ventricular arrhythmias leading to sudden death; and lately has been identified in association with cerebral ischemic events. As yet, no postmorten examinations have been conducted in patients in whom these events have been associated with a prolapsing mitral valve, so that the thromboembolic origin must, for the present, remain conjectural. However, the radiological appearance in the cerebral arteries suggests emboli rather than arterial disease and ulcerative changes have been described on the mitral valve surface at its attachment to the atrium[69] (Fig. 5). Thrombus material has been seen adherent to this lesion, and in other instances, fissuring in the endocardium has been noted, a lesion conducive to platelet and fibrin deposition.[60] Several series have been reported in which prolapsing mitral valve was the only associat-

Figure 1. Left ventricular angiocardiography indicating (arrows) thrombus in an area damaged and rendered akinetic by myocardial infarction two years prior to 3 hemisphere ischemic events. (*From* Barnett, H. J. M.: Pathogenesis of transient ischemic attacks. *In* Scheinberg, P., ed.: Cerebrovascular Diseases. 10th Princeton Conference. New York, Raven Press, 1976, Reproduced by permission.)

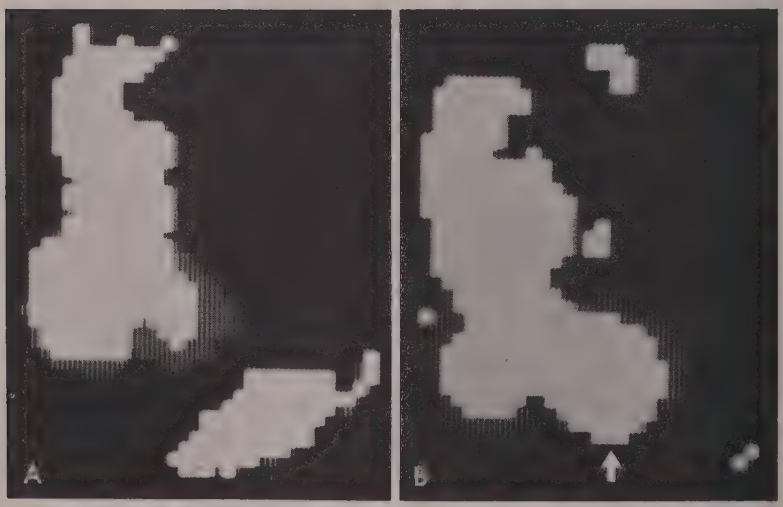

Figure 2. Wall-motion study of left ventricle ("gated synchronous acquisition") indicating (*A*) normal diastolic filling (hatched) extending beyond normal systolic filling (solid white), and (*B*) the superimposition of shadows at apex (arrow) where postinfarction akinetic segment resulted in cerebral thromboembolism after 6 months. (Courtesy of Dr. M. Chamberlain.)

Figure 3. Nonbacterial vegetation, largely of platelets and fibrin, attached to mitral valve in patient with recurrent ischemic events.

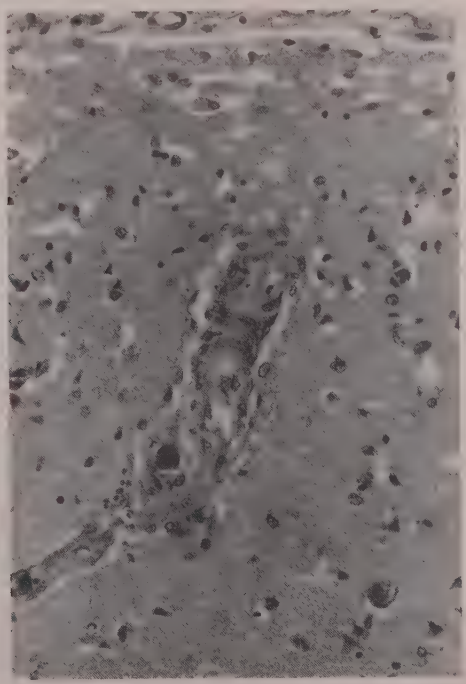

Figure 4. Embolus in cerebral arteriole from same case as Figure 3.

Figure 5. Myxomatous degeneration of mitral valve with thrombus attached to ulcerative lesion (arrow) at atrial attachment which was the site of thrombus at fresh post-mortem examination. (*From* Silver, M., in Edwards, J., Lev, M., and Abel, M. eds.: The Heart. Baltimore, Williams and Wilkins, 1974, pp. 87–109. By permission.)

ed abnormality which would account for the cerebral ischemic event(s).[5, 6, 28, 34, 42, 80]

In younger patients, the usual prevalence of prolapsing mitral valve by M-mode echocardiography is between 5 and 10 per cent.[58] A similar prevalence was determined in a study of an older population (average age 68) and a similarly aged control population of patients with stroke and threatened stroke. By contrast, in a series of 60 patients, 45 years and under (average age 33) who had stroke and/or a transient ischemic attack, this cardiac defect was seen in 40 per cent.[6] Prolapsing mitral valve has an occasional familial incidence. The writer knows of three families, one of which has been published,[64] with a striking incidence of familial strokes in young patients in conjunction with familial prolapsing mitral valve and in whom no other source for thromboembolism has been identified. In summary, it is difficult to deny significance to this impressive association, but the final proof awaits postmortem confirmation.

Extracranial Mechanical Interference with Arteries

Osteophytes at unco-vertebral fissures ("neurocentral joints") may interfere with the course of the vertebral artery in patients afflicted with severe cervical spondylosis. It has been established that these may intrude on the vertebral artery with sufficient severity as to produce atheroma and from time to time, symptoms have been attributed to this extracranial compressive phenomenon.[68, 84] Dizziness and non-

specific vertigo have so many other common causes in the population afflicted with spondylosis that one must attribute these symptoms to this mechanism with great care. It would appear to be a singularly rare occurrence. Chiropractic and osteopathic manipulations,[26, 44, 49, 67] and more recently, yoga exercise with neck manipulation,[29] have been identified, most particularly in younger patients, as causes for vertebral artery damage at the C2 level. Damage to the artery either by traumatic dissection or simple endothelial injury appears capable of setting the stage for immediate apoplexy or for the development of events of a recurrent nature, sometimes after a delay. The possibility of platelet-fibrin embolization in such cases is very real (Fig. 6). The association with chiropractic manipulation may be overlooked unless a careful history is elicited. Atlantoaxial subluxations may interfere intermittently with the vertebral artery as it passes through the foramen magnum and produce recurrent ischemic events[37] (Fig. 7). With greater rarity, foramen magnum tumors may interrupt the vertebral artery flow intermittently.

Altered Coagulability; Thrombocytosis

A variety of disorders and some drugs are accompanied by coagulation abnormalities detectable either by routine laboratory tests or in other circumstances by more complex studies. Frequently, an abnormality can be identified, but the challenging problem is to identify, in

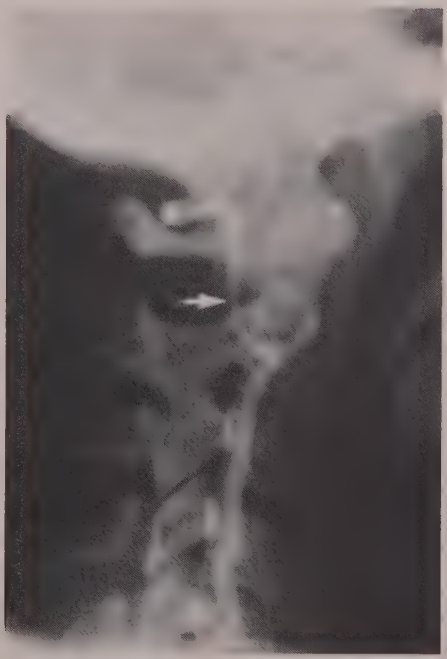

Figure 6. Segment of vertebral artery (arrow) with irregular contour, the presumed site of thromboembolism to vertebral-basilar territory, following chiropractic manipulations in young woman.

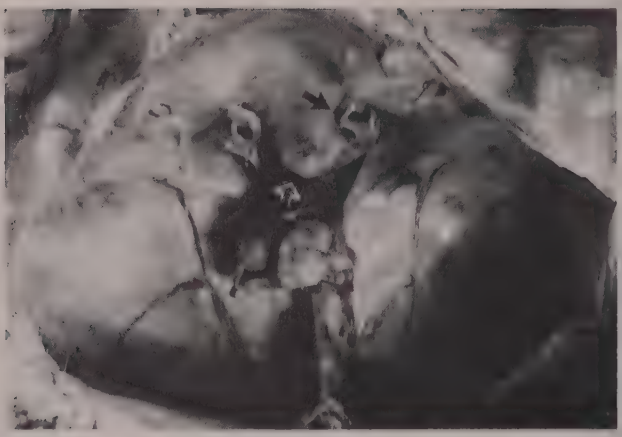

Figure 7. Rheumatoid atlanto-axial subluxation productive of recurrent vertebral basilar ischemic events. Encroachment of odontoid (open arrow) on vertebral artery (closed arrow) clearly visible. (*From* Jones, M. W., and Kaufmann, J. C. E.: J. Neurol. Neurosurg. Psychiatry, 39:122–128, 1976. Reproduced with permission.)

advance, which patient with the recognizable coagulation change will be affected by any clinical symptoms of cerebral thromboembolism. This applies to the use of the contraceptive pill, other estrogen therapy, pregnancy, postpartum and postoperative states, and in patients afflicted with cancer, known or occult.[1] The condition may be heralded by transitory symptoms or may develop as a sudden and dramatic event (Fig. 8). The transient and at times persistent ischemic events known to occur in polycythemia and in sickle cell disease are accompanied by altered viscosity but may be associated with other coagulation abnormalities. Rare examples are on record of paroxysmal nocturnal hemoglobinuria[3] with intermittent cerebral ischemic events related to the hematologic crises.

Thrombocytosis or thrombocythemia occurs in myeloproliferative disorders and as a reactive phenomenon. It is beyond the scope of this paper to provide detailed discussion, save to say that it is usual to find thrombotic tendencies with the former and not the latter. Digital ischemia has featured two reports of cases with increased platelet aggregation as judged by the spontaneous aggregation of the platelets in vitro of 7 thrombocythemic patients.[81, 82] Amaurosis fugax has been observed in idiopathic thrombocythemia and in one, the emboli which had been seen passing through the retina ceased with busulfan (Myleran) and in another with aspirin.[47, 55, 70] Spontaneous aggregation not requiring collagen was noted as well in the latter case and disappeared with aspirin therapy. A recent report describes 5 patients with essential thrombocythemia all with thromboembolism and 2 with transient ischemic attacks. A sixth patient in this series had polycythemia vera with amaurosis fugax and in common with 4 of the other 5 had an increased tendency to spontaneous platelet aggregation.[83]

Other platelet abnormalities have been described in association with transient ischemic attack and stroke. These include enhanced reactivity to aggregating agents, increased glass-bead adhesiveness, increased circulating platelet aggregates, higher levels of platelet coagulant activity, and decreased platelet survival.[15] The reports are conflicting, the laboratory methods are at times unpredictable, and the possibility exists that the abnormalities result from the disease processes and are not causal. To date, no platelet abnormality save thrombocythemia appears to be a good predictor of threatened ischemic events.

Non-Arteriosclerotic Vasculopathies

Particularly in younger subjects, one must consider that ischemic events may be due to a variety of non-arteriosclerotic vascular disorders. These include the curious and occasionally post-traumatic condition of high cervical carotid dissection,[56] granulomatous angiitis, polyarteritis nodosa, disseminated lupus erythematosus, homocystinuria, and fibromuscular hyperplasia. In the Orient and more and more in North America, Moya-Moya disease and some other less common varieties of vasculitis require consideration.

Lacunar Infarction

Lacunes, resulting from hypertensive arteriolar occlusive disease and productive of syndromes reflecting small lesions occurring particu-

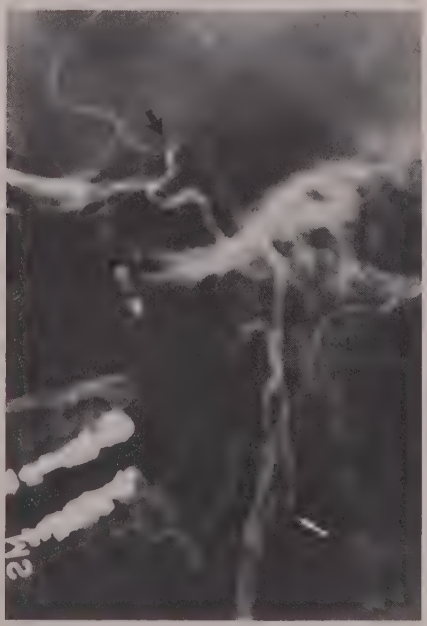

Figure 8. A 26 year old woman suffered stroke after threatening transient ischemic attacks for two days, with thrombus visible (white arrow) in internal carotid artery and embolic obstruction (black arrow) denying flow through middle cerebral artery.

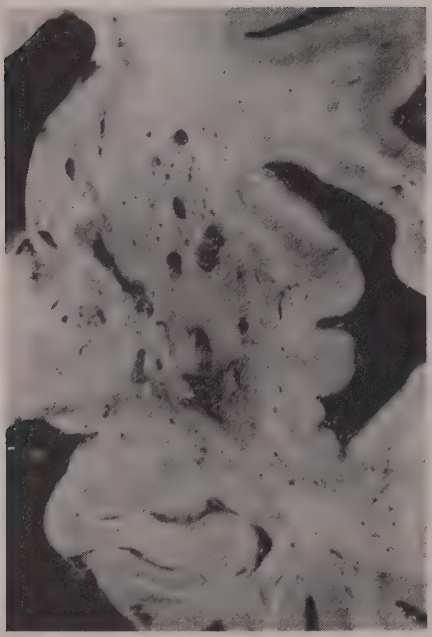

Figure 9. Multiple lacunes in basal ganglia, thalamus, and capsular area in a severely hypertensive individual.

larly in the basal ganglia, internal capsule, and pons, deserve serious consideration in the elucidation of the causes of cerebral ischemic events (Fig. 9). The ischemic event may be sufficiently brief as to mimic transient ischemic attack or reversible ischemic neurological deficit of other origin, or may be a completed partial stroke. The characteristics of these partial strokes have been well recorded and need not be reiterated.[21, 22, 24, 54] In the largest comparative series available in the modern literature, 23 per cent of 131 lacunar strokes and 50 per cent of 233 arterial thrombotic lesions causing strokes had premonitory transient ischemic attack.[53] Lacunes demand consideration in all patients under suspicion for transient ischemic attack.

Artery-to-Artery Emboli

Much of the work of the past three decades attempting stroke prevention with antithrombotic agents and with surgical procedures on the arteries of the neck has utilized the concept of thromboembolism originating in the larger arteries, especially the internal carotid artery at the carotid sinus level. The intracranial branches of the artery are the target organs and the retina and brain the sites for the symptoms. In transient ischemic attack presumed to be of this variety, there are appropriate lesions in the extracranial arteries in the majority of the cases of carotid origin. The data from the Canadian Cooperative Drug Trial indicated that 78 per cent of the first 276 cases with carotid symptoms entered into this study of transient ischemic attack and par-

tial stroke had detectable lesions appropriate to the symptoms.[2] Significant (greater than 30 per cent) stenosis and ulcerative atheroma were the commonest lesions, being seen in 35 and 27 per cent respectively. "Other atheromas" were seen in 7 per cent, occlusion in 13 per cent and intracranial lesions alone in 2 per cent. The majority of the serious lesions involved the extracranial course of the internal carotid artery.

It has been stated that there may be major differences between the pathogenesis of carotid and vertebral-basilar transient ischemic attack. While there may be some truth in such a statement, the more carefully one excludes cardiac sources in accounting for vague brain stem and diffuse symptoms, and takes care to exclude possible lacunar infarction, the less one encounters normal vertebral-basilar arteries in transient ischemic attack and partial stroke of vertebral-basilar origin. The Canadian study, indeed, had fewer normal angiograms in the vertebral-basilar cases than in the carotid cases (Table 1). When symptoms occurred in both arterial systems, there was even less probability of normal arteries related to the symptoms and signs.

The artery-to-artery embolic material is recognized now as being of two types: both platelet-fibrin and also debris from atheromatous ulcerative lesions. The latter may be no more than cholesterol crystals (Fig. 10), or it may be a mixture of cholesterol with other gummous

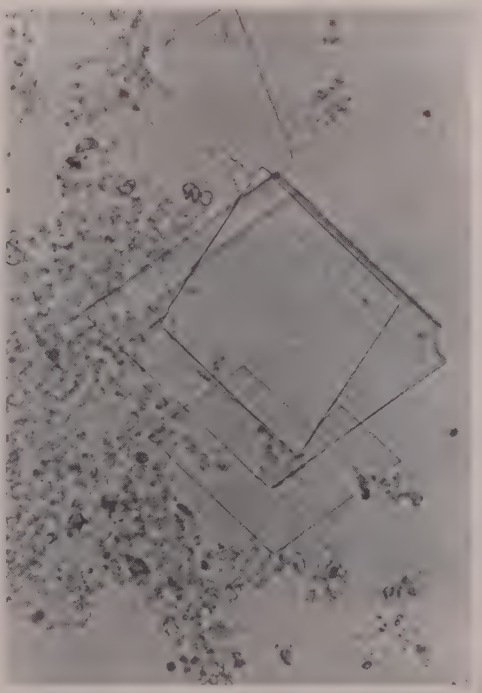

Figure 10. Cholesterol crystals and platelet debris washed from base of an atheromatous ulcer in the internal carotid artery. (Courtesy of Dr. J. C. E. Kaufmann.)

Table 1. *Correlation of Angiographic Findings with Symptom-site*

	CAROTID	VERTEBRO-BASILAR	BOTH
Total	276	75	43
Appropriately "abnormal"	78%	82%	86%
More than one appropriately "abnormal"	35%	43%	47%
"Normal" appropriate to symptoms	22%	17%	14%

material and fragments of necrotic intima. The frequency with which the different mechanisms produce threatened stroke in the population at risk cannot be stated precisely. The retina is an excellent mirror of artery-to-artery emboli, but the platelet-fibrin variety of embolus passes on often in a few minutes, and leaves no trace. Occasionally, one is fortunate enough to be there with an ophthalmoscope as the amaurosis fugax comes and goes. Even more rarely will the opportunity present itself to the clinician to observe the passage of such material into cerebral arteries and arterioles. A remarkably fortuitous circumstance did produce such an opportunity as illustrated (Figure 11). By contrast, the "bright plaque" may remain for hours, days or weeks and may be replaced by a "dead white" sheath of fibrous scar about the arteriole. This persistence allows this type of lesion to be observed more regularly. Its counterpart in the cerebral arteries must be sought by most careful pathological inspection (Fig. 12).

Hard pathological data is lacking but the best evidence at the present time appears to be that transient ischemic attack, reversible ischemic neurological deficit and partial nonprogressing stroke more commonly result from artery-to-artery emboli than from all other causes.

Figure 11. *A*, White embolus, presumably platelets (open arrow), and fibrin passing through a small cortical middle cerebral artery at EC/IC operative exposure. *B*, Seconds later, the same artery is clear of thrombus (closed arrow).

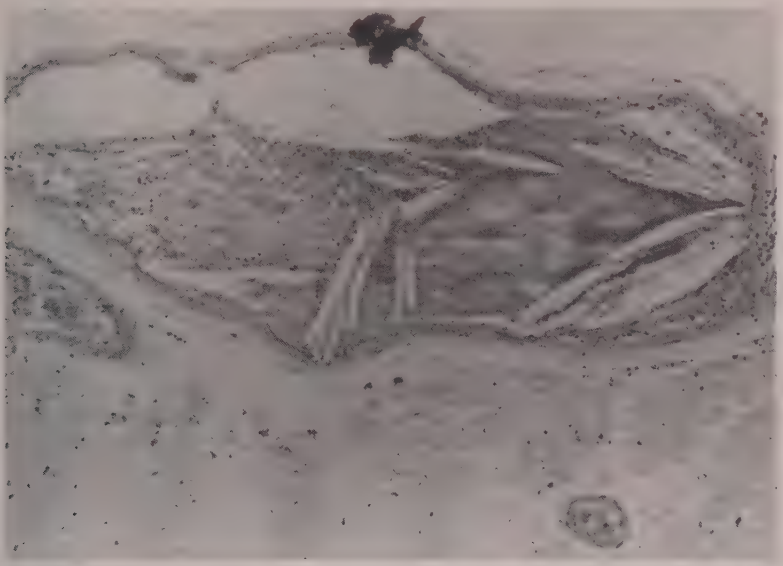

Figure 12. Cholesterol and thrombus-containing cortical artery in patient dying after multiple thromboembolic ischemic events.

Cardiac emboli emerge as the next most common causes with lacunar infarction occupying third place.[53] Thought must always be given to the possibility of the occurrence of the other varieties in any given instance, but their incidence ranks well behind the other three.

PROGNOSIS IN TRANSIENT ISCHEMIC ATTACK

Ideally, one would like to know the prognosis for each of the particular varieties of stroke and threatened stroke. In the foreseeable future, this may be an attainable goal. At the present time, much of what is known about prognosis has been obtained from series which have considered transient ischemic attacks as a whole and have not allowed for the separate identification of the varieties. Since they have different mechanisms, it is apparent now that they must have different prognoses.

In the meantime, we are left to know that in general, the risk of stroke in a patient who has had a transient ischemic attack is in the neighborhood of 5 to 6 per cent a year.[27] It is also known that the risk is greatest in the first 3 months after the first transient ischemic attack.[79] Death in the generic group of disorders, including unquestionably some cardiac causes, is more commonly the direct result of cardiac disease with stroke as the second cause. There is some evidence that in patients with bright plaques in the retina the prognosis is worse than in the others. A survival study indicated that 15 per cent

were dead within one year and 54 per cent dead in the 7 years of follow-up of 208 cases.[59]

SYMPTOMATOLOGY OF TRANSIENT ISCHEMIC ATTACKS

The common symptoms which reflect threatened stroke have been worked out and need not be detailed here. Tables 2 and 3 summarize symptoms experienced in a study of transient ischemic attacks and partial stroke. It is important to recognize that certain isolated symptoms, even when they are recurrent, and probably particularly when they are recurrent over a long period of time, cannot be attributed to cerebral ischemia. Isolated or recurrent episodes of vertigo, nonspecific dizziness, episodes of loss of consciousness, diplopia, drop attacks, and amnesic episodes must be attributed to ischemia with great caution. Each of these symptoms will occur within the framework of a concatenation of symptoms making up ischemic episodes in vertebral-basilar territory. It is not possible however, to attribute them to ischemia when they occur as single symptoms. More protean and more common causes may be the explanation in individual cases. Such patients should be spared the possible hazards attendant upon investigation and treatment of events that could reasonably be expected to be part of the work-up of patients with more definite retinal and cerebral ischemia.

INVESTIGATIVE PROCEDURES

Investigation of transient ischemic attack and other cases of threatened stroke requires concern for the possible pathogenetic mechanisms. It may be misleading to assume that a particular etiology exists in any given case without a review, at times cursory, at other times detailed, of the various possibilities itemized earlier in this paper. No ritualistic approach should be recommended in investigation any more than a cookbook type of therapeutic approach should be set down. The usual patient with amaurosis fugax ipsilateral to a carotid bruit, and with appropriate hemispheric symptoms and signs, should be investigated first by ordinary attention to the blood and cardiovascular system. Then, if there is diagnostic doubt or the possibility exists of a surgical approach (not likely in the frail and very elderly) patients ought to be considered for angiography. The younger patient should be studied in the same way, but if the angiogram is normal, very special and detailed cardiac studies may be appropriate, having in mind the mechanisms and abnormalities referred to above. The symptoms and signs of significant hypertension should be studied with lacunar infarction syndromes in mind. The CT scan, albeit negative for most lacunar lesions, can be a helpful adjunct in this type of case. It need scarcely be stated that the CT scan is the indispensable diagnostic procedure in the diagnosis of hemorrhage.

Table 2. *Carotid Artery Transient Ischemic Attacks: Presenting Symptoms in 133 Patients**

SYMPTOMS	PER CENT OF PATIENTS
Paresis (mono, hemi)	61
Paresthesia (mono, hemi)	57
Monocular visual	32
Paresthesia (facial)	30
Paresis (facial)	22
Dysphasia	17
Dysarthria	16
Headache	12
Lightheadedness	3
"Dizziness"	3
Convulsion (focal)	3
Convulsion (grand mal)	3
Binocular visual (hemianopia)	3
Visual hallucination	3
Dysphagia	3
Mental change	3

*From Genton, E., and Barnett, H. J. M.: Stroke, 8:147–157, 1977. By permission.

Table 3. *Vertebral-Basilar Transient Ischemic Attack: Presenting Symptoms in 54 Patients**

SYMPTOM	PER CENT OF PATIENTS
Binocular visual	57
Vertigo	50
Paresthesia	40
Diplopia	38
Ataxia	33
Paresis	33
"Dizziness"	20
Headache	18
Nausea/vomiting	14
Dysarthria	14
Loss of consciousness	14
Visual hallucination	7
Tinnitus	5
Mental change	5
Dysphasia	3
"Drop attacks"	3
Drowsiness	3
Lightheadedness	3
Hearing loss	3
Hyperacusis	3
Dysphagia	3
Weakness (generalized)	3

*From Genton, E., and Barnett, H. J. M.: Stroke, 8:147–157, 1977. By permission.

In the past few years, considerable time, money, and energy have been expended on the development of noninvasive techniques said to be useful in evaluating lesions in the carotid artery in the neck. Visualization of the bifurcation region by echocardiographic techniques has given reliable values in approximately one third of patients, satisfactory observations in another third, and unsatisfactory studies in another third of those studied. Other techniques which have been employed include orbital plethysmography, ophthalmodynamometry, thermography of the periorbital and frontal areas; and this list, with various refinements, grows each year. Some observers have felt that combinations of these tests can give a reliable index of the degree of stenosis and that they are particularly valuable in cases of carotid occlusion.

The major problem, however, is the correct application of these techniques.[65] Their use in patients with asymptomatic carotid bruits raises the question of subsequent surgery in this group who are not at any greater risk of stroke than an age-matched entirely asymptomatic population.[39] Similarly, their use in the study of carotid arteries contralateral to symptomatic vessels where the eventual purpose is to perform surgery raises the question of risk-benefit ratio of such surgery on vessels which are "asymptomatic". The risk of stroke from asymptomatic vessels with evidence of stenosis is small. Despite a few enthusiasts, there is considerable accumulation of evidence raising serious doubts about this attack on asymptomatic arteries.[36, 46]

A singularly unsubstantiated concept has been advanced of serious danger to the brain from drop in blood pressure occurring in an individual with neck bruits who must undergo major surgery. This hypothesis has been used to justify the use of noninvasive studies with a view to later angiography and operation on asymptomatic stenoses, as a prelude, most particularly, to aortic and heart surgery. This practice is in conflict with much of the data presented above, it is poorly documented by good clinical observations, and good studies cast it in a most dubious light.[10, 18, 75]

Where transient ischemic attacks are clearly present, use of noninvasive methods to screen out the patients with no evidence of carotid stenosis would appear at first glance to be valuable. On the other hand, small nonstenosing plaques which are feeding emboli into the carotid circulation might be missed at the present level of technology.

An exciting prospect for the future could be the development of a predictable capability of identifying thrombi by the radionuclide tagging of platelets or fibrinogen.[15] Thrombi, actively incorporating platelets or fibrinogen, may be present in neck arteries causing continuing symptoms in progressing stroke, may be present in the "stumps" of internal carotid arteries,[8] may be filling ulcer "craters" in carotid arteries, may be on heart valves or in heart chambers and may be in that most elusive area for all present methods of investigation, the atheromatous lesions of the ascending aorta. The use of radioactive gallium or indium or subsequent generations of tracers will allow these studies to be exploited further once the technology has been perfected.

THERAPY OF THREATENED STROKE

Since cerebral ischemic events have a variety of causes, it is apparent that no single therapeutic program can be expected to prove effective for all cases. An exception to this statement is the importance to be attached to the elimination of *risk factors*. The increased risk of stroke in the hypertensive individual demands its vigilant therapy and this treatment possibly represents the most important single factor that can be applied in prevention of stroke. Although other risk factors are important, some, such as cigarette smoking, appear to operate to a lesser extent in cerbral than in coronary artery disease; some such as hyperlipidemia do not appear to be as responsive to therapy; and at least one, heredity, cannot be changed.

Specific therapy plainly is indicated for a variety of conditions which may forewarn of stroke. The physician must consider carefully the possibility that the case in question may represent one of the great variety of conditions recorded above, and apply the appropriate treatment. A cardiac pacemaker may be indicated. Antihypertensive therapy may need adjusting to correct orthostatic hypotension, or may need to be instituted as in lacunar infarction. Cardiac emboli may require anticoagulation or nonarteriosclerotic vasculopathies may require steroid drugs.

If it is concluded after careful study that the patient is affected with cerebral arterial disease and is afflicted with thromboembolic phenomena of arterial origin having what have been dubbed "artarems,"[32] the therapeutic possibilities are narrowed, and *antithrombotic* therapy will require consideration. The following reasons are cogent in deciding that the patient may benefit from *platelet antiaggregants*:

1. Antispasmodic agents have not been proven to be of any significant value. Their rationale was based on the erroneous premise that vasospasm was an important part of threatened stroke or that vasodilatation could effectively improve cerebral circulation and reduce the risk of stroke. Convincing clinical evidence in this area is totally lacking, and antispasmodics do not appear to have any useful place in the patient threatened with stroke.

2. Anticoagulants will be the subject of Dr. Millikan's separate discussion. However, their administration to patients with cerebral ischemia from arterial thromboembolic disease has not been demonstrated in the stroke-threatened patient to prevent stroke or death by means of a well-designed scientific study. This does not mean that there is no indication for their use but that their usefulness is limited and their impact on the problems of total stroke and threatened stroke problem is disappointing.

3. Thromboendarterectomy again will be discussed separately by Dr. Robertson. Suffice it to say that statistically acceptable proof that stroke and death from stroke is less likely to occur in patients submitted to thromboendarterectomy compared to those treated by conservative means has not been forthcoming. As has been noted, "it is not

that we *should not operate* on stroke-threatened patients, but the evidence does not indicate that we are *obliged to.*"[45] The advent of treatment for risk factors and platelet-inhibiting therapy, indeed, may cast further doubt in this area of uncertainty. It is certain that angiographic investigation of stroke-threatened patients carries a risk in the very best of experienced hands.[19] This, when added to the small but definite risk of complications even by most skilled surgeons, directs that the procedure of thromboendarterectomy be regarded with caution, carried out only by experts, and, ideally, performed when skilled neurologic surveillance constitutes part of the team. There will remain a large number of patients for whom it is not to be recommended.

4. The role of platelets in thromboembolic disease has been clearly demonstrated. Arterial injury from whatever cause, including arteriosclerosis, has been shown to result in platelet adherence, release of platelet contents and platelet aggregation. Platelet-fibrin emboli have been identified in the retinal arterioles by direct vision and pathologically and have been photographed passing through cerebral arteries. Emboli of cholesterol crystals and of atheromatous debris have been photographed in the retinal arterioles (Figs. 13 and 14). They are known to precipitate an extending type of platelet-induced thrombosis[70] (Fig. 15).

5. Drugs which interfere with platelet function are available and safe for administration to human subjects. In Mustard's laboratory, the reduction of platelet adhesiveness and prolongation of platelet survival with the uricosuric agent, sulfinpyrazone, was the first

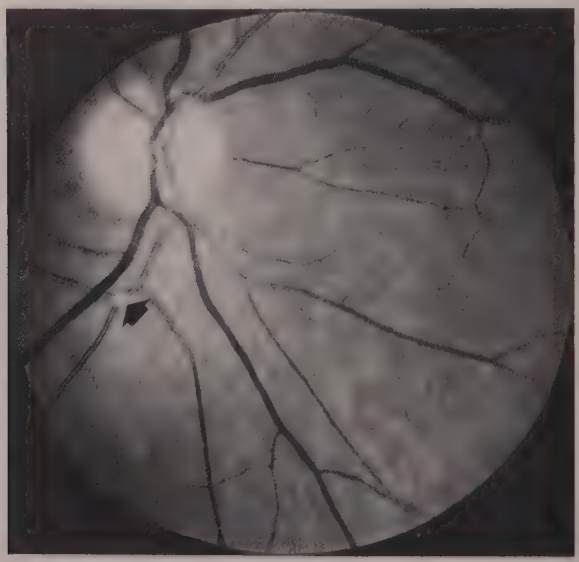

Figure 13. Cholesterol crystal (arrow) in retinal arteriole associated with amaurosis fugax. (Courtesy of Dr. J. Murray.)

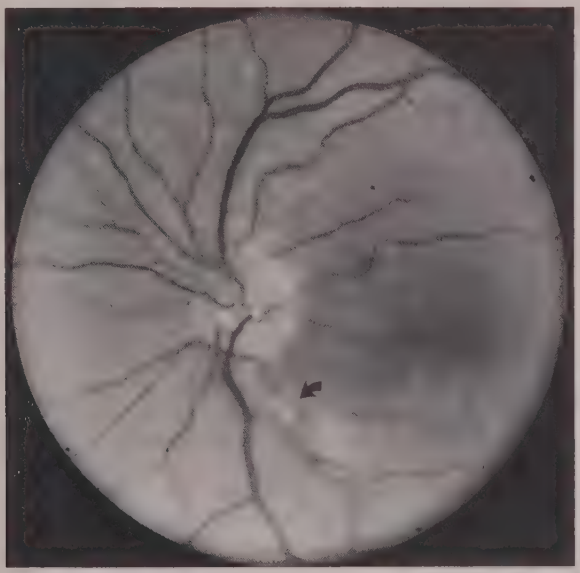

Figure 14. Yellowish atheromatous debris (arrow) lodged in retinal arteriole. Three months later, no abnormality remained.

Figure 15. Rabbit's artery filled with thrombus initiated by intraarterial injection of cholesterol and atheromatous debris. Note cholesterol crystals scattered through thrombus in scanning EM photo. (*From*: Barnett, H. J. M.: A randomized trial of aspirin and sulfinpyrazone in threatened stroke—The Canadian Cooperative Study Group 11th Princeton Conference. Raven Press, in press. Reproduced with permission.)

breakthrough here.[71] Shortly thereafter, the antiplatelet properties of the pyrimidopyrimidine compound, dipyridamole, were demonstrated.[17] Within a year, it was determined that aspirin inhibited platelet activity.[78] It is probable that aspirin and sulfinpyrazone act by slightly different mechanisms but both are effective as inhibitors of cyclooxygenase, the enzyme necessary for conversion of the arachidonic acid formed from the phospholipid of the platelet membrane into prostaglandins and thromboxanes. Without prostaglandin (PGG_2 and PGH_2) formation and conversion to thromboxane A_2, release and further aggregation of platelets is interrupted and vasoconstriction does not occur. By a different mechanism of interference with the phosphodiesterase system, dipyridamole exerts an effect resulting, probably, in failure of platelet adherence to injured and diseased arterial surfaces as well as failure of aggregation.[76]

6. Many experimental and some preliminary clinical observations on platelet-inhibiting drugs resulted in consideration being given to their efficacy in cerebral ischemia. An early trial of dipyridamole on a mixed collection of patients yielded negative results.[1] In 1971, a collaborative Canadian trial to test two platelet-inhibiting drugs (aspirin and sulfinpyrazone) was begun. In 1972, a collaborative American trial to test aspirin alone was begun. The results of these two trials have been published[12, 20] and may be summarized in the following way.

The Canadian Trial

The Canadian trial involved 12 cities and 24 hospitals. Patients with transient ischemic attack, reversible ischemic neurological deficit, or partial stroke were eligible for entry with the most recent event required within 3 months of entry into the trial. Patients excluded were those who had unrelated disease likely to lead to death of the patient within the period of the trial (evidence of organ failure, cancer); those who had known intolerance to the trial drugs; those with recent history of peptic ulceration; those whose symptoms appeared to be explained on hemodynamic bases, or were of cardiac origin, or from nonarteriosclerotic vascular disease or associated with known or potential coagulation abnormalities. Randomized separately were patients with carotid and vertebral-basilar symptoms and also patients with transient ischemic attack and persisting symptoms and signs.

Patients were assigned randomly to one of four treatment categories. They received either 1300 mg of aspirin a day in four doses of 325 mg and a placebo instead of sulfinpyrazone; or sulfinpyrazone 800 mg a day in four doses of 200 mg and a placebo instead of aspirin; or both of these active treatment drugs in these dosages; or placebos in place of both these drugs. Precautions were taken and followed throughout the trial to ensure compliance and to avoid contamination. A sample-size calculation estimated that 540 patients would be required to show a benefit if one or other of the drugs would reduce by 50 per cent the probability that 20 per cent of the patients would have a stroke or die within three years. By June of 1976, intake of patients was stopped as

585 patients had been randomized. The patients were then kept on the trial program for one more year. At the end of this time, the data were submitted to analysis.

The average time on the treatment program was 1002 days. Inevitably, some patients were withdrawn and submitted to alternative therapy at the request of their attending or family physicians because of recurrent or persisting symptoms. However, it was possible to maintain the overall population in the study on the treatment program for 92 per cent of the time and to achieve a 99.3 per cent follow-up.

The predetermined endpoints were transient ischemic attack, stroke, or death, and any of these events which occurred by the conclusion of the trial or within 6 months of withdrawal in those whose treatment was terminated were counted against their treatment regimen. The analysis was done by the log-rank life-table method particularly adapted to a study of a group of patients placed in different therapeutic programs and followed for a prolonged period of time.[58] The results indicated that the combination of the three endpoints (transient ischemic attack, stroke and death) was reduced by 19 per cent ($P<0.05$), in patients taking aspirin compared with no significant benefit for those taking sulfinpyrazone (Fig. 16). For stroke and death alone, the reduction with aspirin was 31 per cent ($P<0.05$), again without benefit from sulfinpyrazone (Fig. 17). The unexpected finding in subset analysis was that all the benefit from aspirin therapy was in men, in whom there was a 48 per cent reduction in stroke and death ($P<0.005$), while there was no significant benefit in women (Fig. 18). If stroke and stroke-death were considered alone, there was a 49 per cent reduction in men ($P<0.004$) and a negligible effect in women on aspirin, and again no significant benefit from sulfinpyrazone.

The design of the study was such that it was important to determine if there was synergism or antagonism between the two active

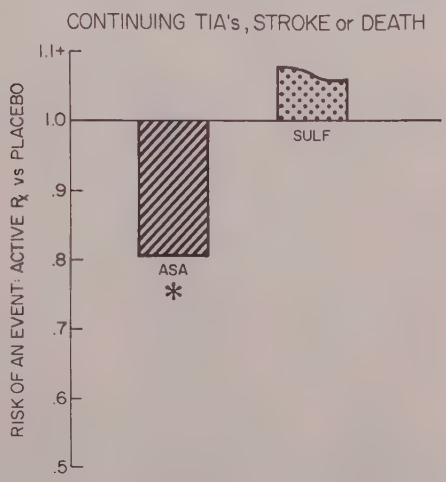

Figure 16. Significant (*) reduction in three end-points in Canadian Cooperative Study, indicating 19 per cent reduction with aspirin (ASA) and nil significance with sulfinpyrazone (Sulf).

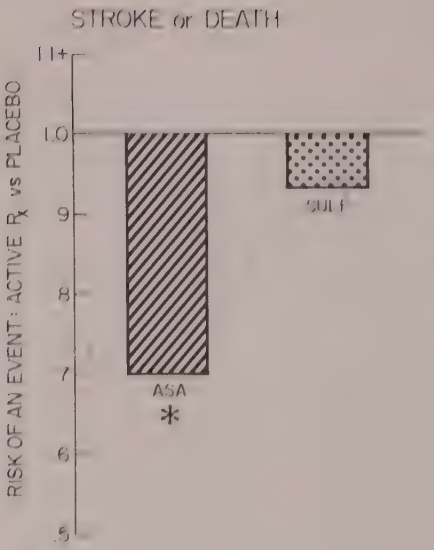

Figure 17. Significant (*) reduction in stroke or death in Canadian Cooperative Study, indicating 31 per cent reduction with aspirin (ASA) and nil significance with sulfinpyrazone (Sulf).

drugs. This was not found to be the case in a significant fashion so that one-half of the cases whose treatment included aspirin were legitimately comparable with the one-half of the cases whose regimen included sulfinpyrazone (Fig. 19).

Looking at first events in males and females and not considering a life-table analysis type of assessment, there were 20 strokes in the

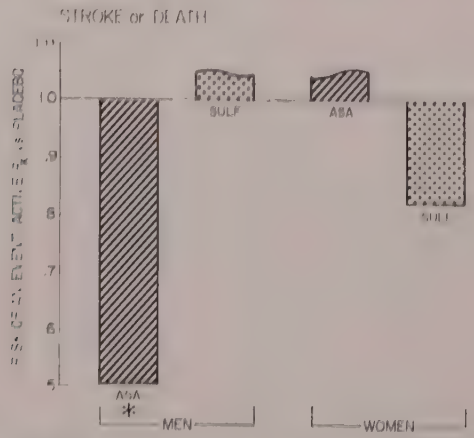

Figure 18. Significant (*) reduction in stroke or death in male but not in female patients with aspirin (ASA). A 48 per cent reduction in men, no benefit in women and nil significance for either sex with sulfinpyrazone (Sulf).

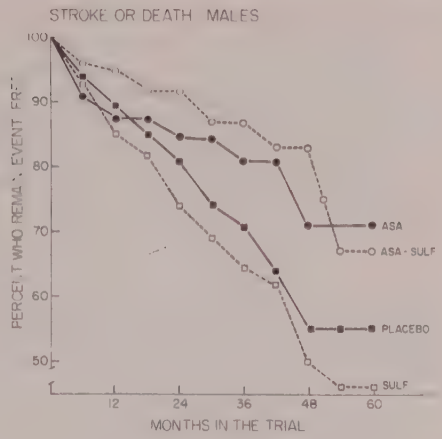

Figure 19. The lack of benefit of sulfinpyrazone (Sulf), the benefit of aspirin (ASA), and the lack of synergism or anatagonism between the combination of aspirin and sulfinpyrazone in the Canadian Cooperative Study.

men taking aspirin, compared to 40 in those not taking aspirin. Similarly, additional vascular episodes were twice as common in the men not taking aspirin as in those not taking aspirin (Table 4).

By contrast with other reported transient ischemic attack series, the vascular deaths were more commonly from stroke than from myocardial infarction. The reason for this difference presumably relates to the fact that patients in whom there might have been already cardiac emboli as the cause of the cerebral ischemic events were eliminated from the study at the beginning, thereby removing a significant cadre of patients threatened with cardiac death.

The American Trial

The American trial differed from the Canadian trial in several ways. Some of those judged to have "surgical lesions" were unsyste-

Table 4. *First Events in Men and Women With and Without Aspirin*

	WITH ASPIRIN	WITHOUT ASPIRIN
MEN		
Stroke	20	40
Death	9	16
Vascular death	7	11
Stroke and all death	29	56
Stroke and vascular death	27	51
WOMEN		
Stroke	16	9
Death	1	3
Vascular death	1	3
Stroke and all death	17	12
Stroke and vascular death	17	12

matically eliminated and sent for operation, whereas in the Canadian study, patients with "surgical lesions" were kept in the study. The study period was considerably shorter in that it began in 1972 and was terminated in 1975. A total of 178 cases was randomized and a life-table analysis carried out for a 24-month period. Ten per cent of the cases were lost to follow-up. Entrants had symptoms in carotid territory and those with vertebral-basilar symptoms were excluded unless carotid symptoms were also present. The results of the 24 month analysis indicated no significant reduction of stroke and death with aspirin, but when these results were coupled with occurrence of transient ischemic attack in the first 6 months, there was a favorable response to aspirin. For these three endpoints of transient ischemic attack, stroke, and death combined in this manner, there was a statistically significant differential ($P \leq 0.01$) in favor of aspirin. No difference between the response of men and women was presented but the numbers were too small to make a convincing statement here.

SUMMARY COMMENT ON THE USE OF PLATELET-INHIBITING DRUGS IN THREATENED STROKE

1. The two randomized trials support the hypothesis which had been developed from a wealth of experimental data and a scattering of anecdotal clinical information, that for transient ischemic attack, reversible ischemic neurological deficit and partial stroke, aspirin is of significant benefit to men in preventing stroke and vascular death including stroke-death.

2. Data are not available and neither of the randomized studies examined the question of platelet-inhibiting drug therapy for a group of patients with transient ischemic attack and partial stroke lumped together where cardiac causes, lacunar infarctions, coagulation disorders, hemodynamic mechanisms, etc., might have been the cause. The known data can be applied only to therapy for threatened stroke which is thrombo-embolic from arteriosclerosis of the cerebral arteries. The results cannot be considered comparable to other treatment trials where patients with stroke of diverse causes have been considered together.

3. To date, no other treatment modality for threatened stroke, in particular neither anticoagulant therapy nor endarterectomy, has yielded results from a randomized double-blind trial with the level of statistical significance found for aspirin.[43] Since all methods other than randomization used in accrediting a treatment regimen leave a great deal to be desired and introduce a great many possible and probably pitfalls, one must be careful not to claim too much edge over other programs for the one treatment regimen which has been assessed with a credible methodology. The other treatments may be as valuable but we simply cannot tell!

4. With the exception of thromboembolism associated with thrombocythemia,[83] a rare condition, no treatment program utilizing platelet

antiaggregants has been reported to show a clear benefit for women. Negative results in women, despite benefit for men, have been reported from other studies. These include aspirin in venous thromboembolism,[31] sulfinpyrazone in dialysis shunts,[38] the Canadian stroke study,[12] and most recently, some suggestive evidence from a retrospective survey of long-term aspirin usage in patients with rheumatoid arthritis showing a reduction, in men, of coronary thrombosis and stroke.[18] Experimental evidence is available linking thrombogenesis to sex-related factors[81] and the benefit of aspirin in mechanically produced thrombogenesis in male but not in female rabbits has been reported in a well-controlled study.[40]

5. The dosage and type of aspirin therapy will require further study. The dosage of aspirin effective in these trials, 1300 mg daily, probably is not sufficient to inhibit the cyclo-oxygenase system in the endothelial cells lining the arteries. If it were, it would, of course, inhibit the beneficial production of prostacyclin (PGI_2), a powerful antiaggregant and vasodilator. A smaller dosage of aspirin might be effective in its antiplatelet aggregation effect in stroke prevention but this amount of drug has not been subjected to clinical trial. Measurable effect on platelet aggregation in vitro persists from 3 to 7 days after a single aspirin tablet has been ingested.[77] Recent studies confirm that enteric-coated aspirin is an effective platelet antiaggregant, which gives delayed but reasonable blood levels of acetylsalicylic acid.[50]

The interference with the ability of circulating platelets to initiate endoperoxide synthesis is maximal up to 8 hours after absorption. Cyclo-oxygenase enzyme activity has begun to recover and has reached 10 per cent of control within 24 hours.[50] The suggestion from this data is that the megakaryocytes are not affected by the drug and that they are ready to produce active platelets which appear in sufficient quantities to be detectable in about 8 hours. A preliminary conclusion from this study may be that a once-daily or even a twice-daily dose schedule may not be sufficiently frequent. More work here is needed.

6. Aspirin produced upper gastrointestinal distress in about 15 per cent of patients in the usual platelet-suppressing dosage. Nevertheless, in the Canadian trial, no hematemesis or melena occurred despite the fact that close to 300 patients ingested 1300 mg daily over an average period of approximately 3 years. For some patients who have gastrointestinal distress, the enteric-coated form will provide relief. Recent observations indicate that the concomitant administration of cymetidine will allow many patients to take aspirin despite symptoms indicative of peptic ulceration.[33]

7. Combinations of aspirin with yet other platelet-inhibitors may prove more effective than aspirin alone. There is some experimental evidence to support the possible synergistic benefit of dipyridamole added to aspirin at least in terms of the effect on platelet survival.[30] A collaborative trial of these two agents is being undertaken in Canada and the United States at the present time.

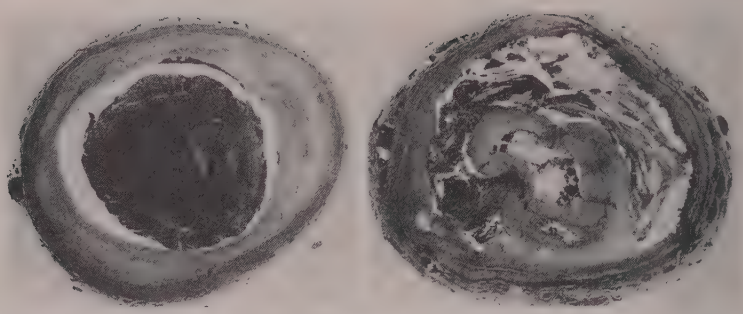

Figure 20. *Left.* Rupture into an atheromatous plaque in the basilar artery just beyond its origin. *Right.* Fresh thrombus filling (save for retraction artefact) the lumen of the distal basilar artery.

8. Aspirin is far from the ultimate and ideal therapy for the prevention of stroke. In the Canadian trial, 20 men suffered a stroke despite its administration, and females did not benefit at all. The value of this platelet antiaggregant was particularly disappointing in cases with symptoms occurring in both the carotid and vertebral-basilar territory at the same time, and in those with angiographic evidence of extensive involvement of a large number of the cerebral arteries.[13] These two observations suggest that by the time more widespread and therefore more serious atheroma has developed, the benefit to be expected from platelet-inhibition may be disappointingly small.

9. Some of the consequences of atheroma, such as rupture of a plaque (Figure 20) and haemorrhage into a plaque with rupture into the lumen, will yield sufficient stimulus to the coagulation process by tissue-factor (thromboplastin) production that platelet anti-aggregant therapy might readily be overwhelmed.

10. The primary goal in stroke prevention must remain that of eliminating atherogenesis.

11. Platelet anti-aggregant therapy, although it may yet be shown to have some benefit in reducing the tendency to atherogenesis, has not been studied in this way, and large-scale trials would be required before this could be regarded as more than an intriguing hypothesis.

REFERENCES

1. Acheson, J., Danta, G., and Hutchinson, E. C.: Controlled trial of dipyridamole in cerebral vascular disease. Brit. Med. J., *1*:614–615, 1969.
2. Barnett, H. J. M.: A randomized trial of aspirin and sulfinpyrazone in threatened stroke — The Canadian Cooperative Study Group. 11th Princeton Conference, 1978.
3. Barnett, H. J. M.: Pathogenesis of transient ischemic attacks. *In* Scheinberg, P., ed.: Cerebrovascular Diseases. 10th Princeton Conference. Raven Press, 1976, pp. 1–21.
4. Barnett, H. J. M.: Platelet and coagulation function in relation to thromboembolic stroke. *In* Thompson, R. A., ed.: Advances in Neurology. *16*:45–70, 1977.
5. Barnett, H. J. M.: Transient cerebral ischemia: Pathogenesis, prognosis and management. Royal College Lecture. Ann. Roy. Coll. Phys. Surg., 153–156, 1974.
6. Barnett, H. J. M., Boughner, D. R., and Cooper, P. E.: Further evidence relating cere-

bral ischemic events to prolapsing mitral valve. Abstract. Ann. Neurol., *4*:163–164, 1978.
7. Barnett, H. J. M., Jones, M. W., Boughner, D. R., et al.: Cerebral ischemic events associated with prolapsing mitral valve. Arch. Neurol., *33*:777–782, 1976.
8. Barnett, H. J. M., Peerless, S. J., and Kaufmann, J. C. E.: "Stump" of internal carotid artery — A source for further cerebral embolic ischemia. Stroke, *9*:448–456, 1978.
9. Barnett, H. J. M., Wortzman, G., and Lougheed, W. M.: Bilateral carotid occlusion. Can. Med. Assoc. J., *95*:1186–1196, 1968.
10. Berkoff, H., and Turnipseed, W.: Postsurgical stroke in cardiac and peripheral vascular disease. Abstract. Stroke, *10*:106, 1979.
11. Brice, J. G., Dowsett, D. J., and Lowe, R. D.: Haemodynamic effects of carotid artery stenosis. Brit. Med. J., 2:1363–1366, 1964.
12. Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. New Eng. J. Med., *299*:35–39, 1978.
13. Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened stroke. Unpublished data.
14. Caplan, L. R., and Sergay, S.: Positional cerebral ischaemia. J. Neurol. Neurosurg. Psychiatry, *39*:385–391, 1976.
15. Claggett, G. P., and Collins, G. J.: Platelets, thromboembolism and the clinical utility of antiplatelet drugs. Surg. Gynec. Obstet., *147*:257–272, 1978.
16. Davis, H. H., Siegel, B. A., Joist, J. H., et al.: Scintigraphic detection of atherosclerotic lesions and venous thrombi in man by indium-III-labelled autologous platelets. The Lancet, *1*:1185, 1978.
17. Emmons, P. R., Harrison, M. J. G., and Honour, A. J.: Effect of a pyrimidiopyrimidine derivative on thrombus formation in the rabbit. Nature, *208*:255, 1965.
18. Evans, W. E., and Cooperman, M.: The Significance of Asymptomatic Unilateral Carotid Bruits in Preoperative Patients. Surgery, *83*:521–522, 1978.
19. Faught, E., Trader, S. K., and Hanna, G. R.: Cerebral complications of angiography for transient ischemia and stroke — Prediction of risk. Neurology, *29*:4–15, 1979.
20. Fields, W. S., Lemak, N. A., Frankowski, R. F., et al.: Controlled trial of aspirin in cerebral ischemia. Stroke, *8*:301–314, 1977.
21. Fisher, C. M.: The arterial lesions underlying lacunes. Acta Neuropath., *12*:1, 1979.
22. Fisher, C. M.: Lacunes: Small, deep cerebral infarcts. Neurology, *15*:774, 1965.
23. Fisher, C. M.: Occlusion of the internal carotid artery. Arch. Neurol. Psych., *65*:346–377, 1951.
24. Fisher, C. M., and Cole, M.: Homolateral ataxia and crural paresis: A vascular syndrome. J. Neurol. Psych., *28*:48, 1965.
25. Fisher, C. M., Ojemann, R. G., and Robertson, G. H.: Spontaneous dissection of cervicocerebral arteries. Can. J. Neurol. Sci., *5*:9–19, 1978.
26. Ford, F. R., and Clark, D.: Thrombosis of the basilar artery with softenings in the cerebellum and brain stem due to manipulation of the neck. Bull. Johns Hopkins Hosp., *98*:37–42, 1956.
27. Genton, E., Barnett, H. J. M., Fields, W. S., et al.: Cerebral ischemia: The role of thrombosis and of anti-thrombotic therapy. Jnt. Comm. for Stroke Resources. Stroke, *8*:147–157, 1977.
28. Hanson, M. R., Hodgman, J. R., and Conomy, J. P.: A study of stroke associated with prolapsed mitral valve. Abstract. Neurology, *28*:341, 1978.
29. Hanus, S. H., Homer, T. D., and Harter, D. H.: Vertebral artery occlusion complicating yoga exercises. Arch. Neurol., *34*:574–575, 1977.
30. Harker, L. A., and Slichter, S. J.: Arterial and venous thromboembolism: Kinetic characterization and evaluation of therapy. Thrombos. Diathes. Haemorrh., *31*:188, 1974.
31. Harris, W. H., Salzman, E. W., Athanasoulis, C. A., et al.: Aspirin prophylaxis in venous thromboembolism after total hip replacement. New Eng. J. Med., 297:1246–1249, 1977.
32. Hass, W. K.: Occlusive cerebrovascular disease. MED. CLIN. N. AMER., *45*:1281–1297, 1972.
33. Hass, W. K., and Hazzi, C.: Cimetidine protection against gastric side effects of long term therapy for TIA. Excerpta Medica, 1979, (in press).
34. Hirsowitz, G. S., and Saffer, D.: Hemiplegia and the billowing mitral leaflet syndrome. J. Neurol. Neurosurg. Psychiatry, *41*:381–383, 1978.
35. Hultquist, G. T. J.: Ueber Thrombose and Embolie der Arteria carotis. Stockholm, Norstedt, 1942.
36. Humphries, A. W., Young, J. R., Santilli, R. N., et al.: Unoperated, asymptomatic significant internal carotid artery stenosis: A review of 182 instances. Surgery, *80*:695–698, 1976.
37. Jones, M. W., and Kaufmann, J. C. E.: Vertebrobasilar artery insufficiency in rheumatoid atlantoaxial subluxation. J. Neurol. Neurosurg. Psychiatry, *39*:122–128, 1976.

38. Kaegi, A., Pineo, G. F., Shimizu, A., et al.: Arteriovenous-shunt thrombosis — Prevention by sulfinpyrazone. New Eng. J. Med., 290:304–306, 1974.
39. Kagan, A., Popper, J., Rhoads, G. G., et al.: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: Prevalence of stroke. *In* Scheinberg, P., ed.: Cerebrovascular Diseases. 1976.
40. Kelton, J. G., Hirsh, J., Carter, C. J., et al.: Sex differences in the antithrombotic effects of aspirin. Bood, 52:1073–1076, 1978.
41. Kendell, R. E., and Marshall, J.: Role of hypotension in the genesis of transient focal cerebral ischaemic attacks. Brit. Med. J., 2:344–348, 1963.
42. Kostuk, W. J., Boughner, J. R., and Barnett, H. J. M.: Strokes: A complication of mitral-leaflet prolapse? The Lancet, 8033:313–316, 1977.
43. Kuller, L.: The transient ischemic attack: A critical review of anticoagulant and surgical therapy. Stroke, 9:23–26, 1974.
44. Kunkle, E. C., Muller, J. C., and Odom, G. L.: Traumatic brain-stem thrombosis: Report of a case and analysis of the mechanism of injury. Ann. Intern. Med., 36:1329–1335, 1952.
45. Kurtzke, J.: Formal Discussion. *In* Whisnant, J. P., and Sandok, B. A., eds.: Cerebral Vascular Diseases. 8th Princeton Conference. 1974, pp. 190–193.
46. Levin, S. M., and Sondheimer, F. K.: Stenosis of the contralateral asymptomatic carotid artery — To operate or not? Vasc. Surg., 7:3–13, 1973.
47. Levine, J., and Swanson, P. D.: Idiopathic thrombocytosis. A treatable cause of transient ischemic attacks. Neurology (Minneap.), 18:711–713, 1968.
48. Linos, A., Worthington, J. W., O'Fallan, W., et al.: Effect of aspirin on prevention of coronary and cerebrovascular disease in patients with rheumatoid arthritis. Mayo Clin. Proc., 53:581–586, 1978.
49. Lyness, S. S., and Wagman, A. D.: Neurological deficit following cervical manipulation. Surg. Neurol., 2:121–124, 1974.
50. McDonald, J. W. D., Ali, M., Thiessen, J. J., et al.: Plasma acetylsalicylate and salicylate and platelet cyclooxygenase activity following plain and enteric-coated aspirin. Stroke, 1979, in press.
51. McMillan, G. C.: The pathology of cerebral atherosclerosis: A review. *In* Bittar, E. E., and Bittar, N., eds.: The Biological Basis of Medicine. Vol. VI, Chap. 8, 1969, pp. 235–255.
52. Meyer, J. S., Leiderman, H., and Denny-Brown, D.: Electroencephalographic study of insufficiency of the basilar and carotid arteries in man. Neurology, 6:455–477, 1956.
53. Mohr, J. P., Caplan, L. R., Melski, J. W., et al.: The Harvard Cooperative Stroke Registry: A prospective registry. Neurology, 28:754–762, 1978.
54. Mohr, J. P., Kase, C. S., Meckler, R. J., et al.: Sensorimotor stroke due to thalmocapsular ischemia. Arch. Neurol., 34:739, 1977.
55. Mundall, J., Quintero, O., von Kaulla, K. H., et al.: Transient monocular blindness and increased platelet aggregability treated with aspirin. Neurol., 22:280–285, 1972.
56. Ojemann, R. G., Fisher, C. M., and Rich, J. C.: Spontaneous dissecting aneurysm of the internal carotid artery. Stroke, 3:434–440, 1972.
57. Patel, A., and Toole, J. F.: Subclavian steal syndrome: Reversal of cephalic blood flow. Medicine, 44:289, 1965.
58. Peto, R., Pike, M. C., Armitage, P., et al.: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Brit. J. Cancer, 35:1–39, 1977.
59. Pfaffenbach, D. D., and Hollenhorst, R. W.: Morbidity and survivorship of patients with embolic cholesterol crystals in the ocular fundus. Amer. J. Ophthal., 75:66–72, 1973.
60. Pomerance, A.: Ballooning deformity (mucoid degeneration) of atrioventricular valves. Brit. Heart J., 31:343–351, 1969.
61. Preston, F. E., Emmanuel, I. G., Winfield, D. A., et al.: Essential thrombocythaemia and peripheral gangrene. Brit. Med. J., 3:548–552, 1974.
62. Procacci, P. M.: Prevalence of clinical mitral valve prolapse in 1169 young women. New Eng. J. Med., 294:186, 1976.
63. Reed, R. L., Siekert, R. G., and Merideth, J.: Rarity of transient focal cerebral ischemia in cardiac dysrhythmia. J.A.M.A., 223:893–895, 1973.
64. Rice, G. P. A., and Ebers, G.: Familial stroke syndrome associated with mitral valve prolapse. Abstract. Stroke, 10:97, 1979.
65. Sandok, B. A.: Non-invasive techniques for diagnosis of carotid artery disease. Stroke, 9:427–429, 1978.
66. Scheinberg, P., and Stead, E.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. J. Clin. Invest., 28:1163–1171, 1949.
67. Selhorst, J. B., Pevsner, P., Grindal, A. B., et al.: Delayed Sequelae to Vertebral Artery Injury. Neurology 27:360, 1977.

68. Sheehan, S., Bauer, R. B., and Meyer, J. S.: Vertebral artery compression in cervical spondylosis. Neurology, *10*:968–985, 1960.
69. Silver, M.: Rheumatic carditis: Acute and chronic atrioventricular valve disease. *In* Edwards, J., Lev, M., and Abel, M., eds. The Heart. Baltimore, Williams & Wilkins, 1974, pp. 87–109.
70. Singer, G.: Migrating emboli of retinal arteries in thrombocythemia. Brit. J. Ophthal., *53*:279–283, 1969.
71. Smythe, H. A., Ogryzle, M. A., Murphy, E. A., et al.: The effect of sulfinpyrazone (Anturan) on platelet economy and blood coagulation in man. Can. Med. Assoc. J., *92*:818–821, 1965.
72. Spence, J. D., Sibbald, W. J., and Cape, R. D.: Pseudohypertension in the elderly. Clin. Sci. Molec. Med., *55*:399–402, 1978.
73. Sundt, T. M., Whisnant, J. P., Piepgras, D. G., et al.: Intracranial bypass grafts for vertebral-basilar ischemia. Mayo Clin. Proc., *53*:12–18, 1978.
74. Torvik, A., and Skullerud, K.: How often are brain infarcts caused by hypotensive episodes? Stroke, *7*: 255–257, 1976.
75. Treiman, R. L., Foran, R. F., Shore, R. H., et al.: Carotid bruit. Arch. Surg., *106*:803–805, 1973.
76. Warren, B. A., and Vales, O.: Electron microscopy of the sequence of events in the atheroembolic occlusion of cerebral arteries in an animal model. Brit. J. Exper. Path., *56*:205–215, 1974.
77. Weiss, H. J.: Antiplatelet therapy. New Eng. J. Med., *298*:1344–1347, 1978.
78. Weiss, H. J., and Aledort, L. M.: Impaired platelet connective-tissue reaction in man after aspirin ingestion. The Lancet, 2:495–497, 1967.
79. Whisnant, J. P., Matsumoto, N., and Elveback, L. R.: Cerebral ischemia attacks in a community. Mayo Clin. Proc., *48*:194–198, 1973.
80. Wilson, L. A., Keeling, P. W. N., Malcolm, A. D., et al.: Visual complications of mitral leaflet prolapse. Brit. Med. J., 2:86–88, 1977.
81. Uzunova, A. D., Ramey, E. R., and Ramwell, P. W.: Gonadal hormones and pathogenesis of occlusive arterial thrombosis. Amer. J. Physiol., *234*:H454–459, 1978.
82. Vreeken, J., and van Aken, W. G.: Spontaneous aggregation of blood platelets as a cause of idiopathic thrombosis and recurrent painful toes and fingers. Lancet, 2:1395–1397, 1971.
83. Wu, K. Kun-Yu: Platelet hyperaggregability and thrombosis in patients with thrombocythemia. Ann. Intern. Med., *88*:7–11, 1978.
84. Yates, P. O., and Hutchinson, E. C.: Cerebral infarction: The role of stenosis of the extracranial cerebral arteries. Med. Res. Council Spec. Rep. Series, No. 300, 1961.
85. Yufe, R., Karpati, G., and Carpenter, S.: Cardiac myxoma: A diagnostic challenge for the neurologist. Neurology, *26*:1060, 1976.

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The Surgical Management of Extracranial and Intracranial Occlusive Disease

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Although recent evidence indicates a declining incidence in the occurrence of stroke caused by cerebrovascular occlusive disease, stroke still remains the third most common cause of death and the leading cause of disability in North America.[15, 33] There have been considerable advances in the medical therapy of occlusive disease which rely heavily on the control of risk factors, the most important of which is blood pressure control and the administration of anticoagulant and platelet-inhibiting drug therapy. Although the incidence of stroke can be reduced with good medical therapy, surgical therapy is often necessary.[1, 2, 4, 5, 6, 8-11, 13, 18, 20-23, 29, 34, 35]

This gap in medical therapy is emphasized by review of the recent reports of therapy with aspirin. Aspirin appears to reduce the prevalence of stroke in men at risk approximately 50 per cent. Women derive no benefit from this treatment.[1, 2, 10, 11, 24] Several clinical reports indicate that the prevalence of stroke is reduced after surgical therapy for ischemic attacks. Medical treatment is based on the prevention of platelet emboli which often cause stroke or ischemic attacks. However, a number of ischemic attacks reflect inadequate blood flow because of occlusive lesions. The goal of surgery is the prevention of stroke and ischemic attacks by the reconstituting of normal blood flow. This is usually achieved by endarterectomy of cervical stenotic or ulcerated lesions or arterial bypass procedures from extracranial to intracranial vessels.[14, 18, 21, 23, 28, 29, 34, 35] Cervical occlusive lesions are treated by neurosurgeons and vascular surgeons; all of the extracranial-intracranial bypasses are done by neurosurgeons.

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CAROTID ENDARTERECTOMY

The indications for carotid endarterectomy are:

(1) Transient ischemic attacks above a stenotic or ulcerated lesion compatible with the patient's symptoms.

(2) Asymptomatic stenotic lesions:

(a) known severe stenosis prior to other major surgery,

(b) known severe stenosis which may be asymptomatic in a patient who is a good medical risk.

(3) Certain cases of carotid thrombosis.

(4) Spontaneous dissection of the carotid artery which fails to respond to medical therapy or is causing ischemic attacks or progressive stroke is repaired by resection and vein or dacron graft or occasionally by endarterectomy and angioplasty.

(5) The presence of a symptomatic carotid bruit with significant stenosis or ulceration involving the internal carotid artery.[14, 16, 17, 19, 21-23, 25, 26, 28, 29, 35]

The selection of patients for surgical therapy must include rigid criteria and involve a major consideration of the patient's general state of health. The transient attack is a short-lived, painless, focal neurologic deficit relating directly to a cerebral vascular territory and caused by either platelet or atherosclerotic emboli or decreased blood flow. In the carotid territory, these frequently present as amaurosis fugax, speech difficulty, arm, face, and/or leg paresis or numbness. These attacks rarely cause loss of consciousness and should not include vague symptoms, e.g., dizziness or blurred vision.[2, 3, 5, 6, 17-19, 21-23, 30]

The presence of a high-pitched bruit with evidence of decreased pressure or flow ipsilateral to the bruit in a patient on whom major surgery is planned may lead to an arteriogram revealing a high grade carotid stenosis.[5, 6, 9, 14, 22, 23] Many surgeons recommend prophylactic carotid endarterectomy prior to the major surgery.[16, 25] The rationale is based on the possibility of hypotension occurring during the planned surgical procedure with the subsequent development of a cerebral infarction. Although this is common practice and anecdotal cases support the thesis, hard clinical data showing an increased incidence of stroke is not supported by literature review.[8, 12, 32]

The presence of a carotid bruit, which should be sought in routine physical examination particularly in patients over 40 years of age, is an unresolved clinical problem. However, data is available indicating that this bruit may be an ominous sign of a future stroke.[5, 6, 9, 14, 31, 32] Several series of prophylactic surgical repair of asymptomatic carotid lesions are available; however, there is no controlled study proving the best therapy in patients with asymptomatic carotid stenosis. The surgical results of carotid endarterectomy for correction of an asymptomatic carotid stenosis reveal complications of less than 1 per cent.[22, 23, 31] Javid,[5, 6] and in particular Thompson,[31] have series indicating these lesions should be operated. Arteriographic studies of asymptomatic carotid bruits indicate a significant stenosis of the internal carotid artery is

demonstrable in 60 per cent of the arteries. However, there are many other unrelated causes of carotid bruit. The character of the bruit is particularly important in that if it is high-pitched or persists into diastole, it is much more likely to be associated with a significant carotid stenosis.[5, 22, 23, 31] A reasonable approach to the patient with a carotid bruit is to determine whether or not the bruit is associated with decreased retinal artery pressures or cerebral blood flow.[14, 27] If it is, and arteriography confirms a significant stenosis of greater than 60 per cent, and the patient is otherwise a good medical risk, surgery can be recommended. Another seemingly safe approach, supported by Humphries,[12] is to inform the patient of possible symptoms and wait their appearance before arteriography and surgery. A preferred regimen includes careful noninvasive studies. If they show the bruit not interfering with blood flow, the patient should be followed with repeat studies every six months or until he develops symptoms.[14, 27] Atherosclerotic plaques producing the bruit grow at unpredictable rates. Their growth appears to be enhanced in the presence of hypertension. Javid has indicated that two-thirds of the plaques will grow within a two year period; whereas, one-third remain unchanged.[6] The bruit and the implied plaque demands careful evaluation of each individual case and a plan of regular observation.

Occasionally, patients will present with a symptomatic bruit. In this circumstance, noninvasive studies are usually followed by arteriography with subsequent corrective surgery.

Surgical management of the symptomatic occluded carotid artery continues to be controversial. This lesion is best considered in two presentations. The first is the patient who has no symptoms or one or more transient ischemic attacks, but, when seen, has no neurologic deficit or further symptoms. The second is the patient with an immediate or progressive neurologic deficit. In the former, adequate collateral circulation is present, and the main danger to the patient is in the first 10 days to two weeks after the vessel has occluded. This danger is provoked by the distal clot that extends up the internal carotid artery and can possibly propagate into the middle cerebral artery or carotid bifurcation, producing a delayed stroke. Accordingly, this patient should receive heparin for 10 days with subsequent management on platelet-inhibiting drugs for a period of several weeks to allow complete organization of the clot.[23] Some surgeons operate routinely on occluded carotid arteries even in the absence of symptoms. However, there is little support for this approach, because further ischemic events, leaving the course to recommend uncertain. Surgical therapy of cluded artery. The risk of reconstituting an occluded asymptomatic artery surgically is probably as high as the risk of further ischemic events leaving the course to recommend uncertain. Surgical therapy of an occluded carotid that is markedly symptomatic and/or producing a progressive neurologic deficit carries a significant risk. Generally, if the patient is not obtunded and does have a major neurologic deficit, surgical therapy may be indicated when the patient is seen immediately. Occlusion usually presents as a complication of arteriography or in

a patient in the hospital. Surgery carries a significant risk, but the risk appears to be less than the risk of a major cerebral infarct.

Occasionally, spontaneous dissection of the intima occurs in internal carotid arteries. It may occur in the common carotid. The syndrome of spontaneous internal carotid dissection is much less common than atherosclerotic disease. The syndrome has three presentations. The first is the presence of a loud to and fro bruit without further symptoms. The second is the presence of a bruit plus transient ischemic attacks or progressive stroke or neurologic deficit without a bruit, and the last is the presence of a combination of the first two with pain in the neck, head, and behind the eye associated with Horner's syndrome. Medical management of these cases in the absence of a progressing stroke is recommended for 6 to 8 weeks. This consists of anticoagulant therapy with repeat angiography to ascertain resolution. Frequently, the dissection will heal completely. Surgery should not be done unless a significant aneurysmal sac persists as a possible future source of emboli, or the patient has further symptoms.[23, 26]

Carotid endarterectomy is contraindicated or should be considered with considerable hesitation in patients with severe chronic pulmonary disease, a recent myocardial infarction or severe cardiac deterioration. It is also contraindicated in the presence of any life-threatening disease that limits the life expectancy to 6 months.[23]

Clinical Evaluation of the Patient Prior to Carotid Endarterectomy[5, 6, 8, 14, 20, 22, 23, 25, 31]

A careful history and physical examination are mandatory with particular attention to the patient's cardiac status and other hematologic and medical factors that can contribute to the production of transient ischemic attacks. In particular, the patient's tolerance to exercise should be evaluated. Age is not a contraindication to the procedure but the physiologic condition of the patient should be acceptable for surgery. The history and evaluation includes careful attention to regular medication; for example, antihypertensives and diuretics. The serum electrolytes, particularly the serum potassium should be determined and corrected. Intravenous heparin will usually prevent transient ischemic attacks during medical evaluation. The examination includes auscultation and not palpation for carotid or other vascular bruits. Blood pressure in each arm is noted. Appropriate cardiac studies are recommended and, in view of the high incidence of co-existing coronary artery disease, some physicians employ stress testing as a major portion of the cardiac evaluation. If this testing is positive or the patient has frequent anginal attacks, occasional cases may require simultaneous endarterectomy and coronary artery bypass surgery.

Noninvasive studies include oculoplethysmography (OPG), retinal artery pressures and/or Doppler imaging of the carotid bifurcation. Retinal artery pressures are most commonly done. Oculoplethysmography and retinal artery pressures are about 90 per cent accurate in carotid stenosis. However, the definitive study is percutaneous or cath-

eter angiography, which includes at least the symptomatic vessel and, preferably, bilateral carotid and at least one vertebral study combined with an aortic injection.[7, 14, 22, 27] This allows the entire cerebral vascular tree to be outlined prior to operation. Clearly, the failure to evaluate the intracranial vessels is a major error to be avoided in order that other lesions, for example, tumor and/or subdural hematoma, not be overlooked.[23] Computed axial tomography and electroencephalographic testing are often indicated. This regimen gives a clear understanding of the cause of the ischemic events and excludes cerebral mass or seizures.

Preoperative and Postoperative Management[1, 2, 6, 9, 11, 14, 22-25, 31]

The patient requires frequent neurologic checks and careful control of blood pressure. Hypertension should be treated cautiously. If the patient is diabetic, careful medical management of the diabetes is insured. The transient ischemic attacks will almost invariably cease with the administration of intravenous heparin which is best given by constant infusion but can be given intermittently in doses of 5000 to 6000 units every 6 hours. Preoperative sedation is minimized and normal blood volume is maintained by appropriate volume expanders; e.g., 500 ml of serum albumin at the time of induction of anesthesia. Halothane with nitrous oxide and oxygen is probably the anesthesia of choice.

The patient should be placed in a horizontal, supine position with the head and neck postured to allow easy access to the anterior neck. Blood pressure must be maintained at the patient's normal levels. Some surgeons prefer to use intravenous vasopressors to raise the pressure approximately 50 mm Hg to insure adequate cerebral perfusion throughout the procedure. An incision is made along the anteromedial aspect of the sternocleidomastoid muscle with subsequent careful sharp dissection and exposure of the common carotid, external and internal carotid arteries. Wide exposure is recommended prior to intervention into the artery to insure ready access to the plaque. The plaque may extend well up into the internal and external carotid arteries as well as inferiorly into the common carotid artery. Sharp dissection avoids dislodging emboli from the atherosclerotic plaque. The carotid body is blocked with 1 per cent xylocaine solution. Patch angioplasty with either a saphenous vein graft or dacron is recommended in the final repair of the endarterectomy. If dacron is used, a satisfactory graft should be fashioned and preclotted prior to heparinization. Once exposure is satisfactory, vascular clamps or Ramel tourniquets are placed around the common carotid artery proximal to the bifurcation and around the external carotid artery. The superior thyroid artery, if not included in the external carotid ligature, is separately occluded with either ligature or silver clip. The internal carotid artery is occluded with a Ramel tourniquet or a looped 0 suture; some individuals prefer a small, strong aneurysmal clip. The patient receives approximately 5000 to 6000 units of intravenous heparin prior to vessel occlusion. The ligatures are occluded, and the common caro-

tid artery is opened with a sharp pointed knife and then right angle scissors allow arteriotomy from normal intima below through the hard plaque to normal intima into the internal carotid artery.

If electroencephalographic monitoring is used and blood pressure maintained at elevated levels, internal shunting during occlusion can be used on demand. If monitoring is not used, routine shunting with an intraluminal shunt from the common carotid below into the internal carotid artery above is recommended. The plaque is carefully dissected proximally and sectioned at its junction with normal intima, and dissection of the plaque is carried distally up into the external carotid artery and finally peeled out of the internal carotid artery. The vessel wall is meticulously cleaned of all remnants of plaque and debris. The arteriotomy is closed with a running 5–0 or 6–0 monafilament suture which affixes the angioplastic vein or dacron patch, with final removal of the shunt and flushing of the vessels just prior to the last three or four sutures. Subsequently, flow is restored from the common into the external and then into the internal carotid arteries. The heparin is not reversed to prevent the formation of clot at the suture line. The vessel wall is palpated, and, if no thrill is present and pulsation is satisfactory, the wound is subsequently closed. A drain is not recommended.

After wound dressing, the patient is allowed to awaken from anesthesia and carefully monitored, particularly for the first 24 hours. This monitoring should include careful attention to blood gases, blood pressure, and cardiac function. Postoperative retinal artery pressures can be compared to preoperative pressures as a monitor of patency. Neurologic examination is repeated frequently during the first six hours and, subsequently, every hour for the first 24 hours. Blood pressure must be maintained at normal levels for this individual patient, and episodes of hypotension or hypertension rapidly treated. Hypotensive episodes can lead to carotid thrombosis, and hypertension may augment the development of an intracerebral hemorrhage. Oxygen by mask or nasal catheter is recommended for 24 hours. In view of the high incidence of coexistent coronary artery disease, careful cardiac monitoring must be maintained to recognize and treat cardiac arrhythmias or cardiac ischemia. Intravenous fluids are maintained for the first 24 hours and, subsequently, the patient is allowed progressive activity. The first 24 hours of observation must include particular attention to the development of a wound hematoma or a neurologic deficit. Should a deficit occur, the patient should be returned immediately to the operating room, and the wound reopened with careful inspection of the vessel and intraoperative arteriography. If occlusion has occurred, the vessel is reopened.

A special circumstance regarding preoperative medication with platelet-inhibiting drugs, particularly aspirin, is controversial. Ideally, aspirin should be discontinued preoperatively and probably not reinstituted for at least a week. However, some surgeons prefer continuation of platelet-inhibiting drugs. Theoretically, laboratory evidence would

support this approach. However, occasional bleeding problems associated with aspirin therapy can arise, and, if severe, may require platelet transfusions.

Medical therapy does not end with this operation. Medical risk factors, for example, hyperlipidemia, obesity, hypertension, diabetes mellitus, and cigarette smoking, are minimized by continued treatment. Long-term management of the patient with platelet-inhibiting drugs is recommended, particularly for men; their effectiveness in women has not been determined.

Complications[9, 22, 23, 31]

Complications of the procedure include wound hematoma which can be life threatening, producing respiratory obstruction. This may require operative drainage or tracheotomy but must be recognized early to avoid severe respiratory embarrassment. The hematomas present usually as marked wound swelling with subsequent tracheal deviation and local discomfort. However, occasionally, retroesophageal hematomas may present with difficulty in swallowing and speaking with late tracheal compression. Preoperative and postoperative retinal artery pressure monitoring supports a patent artery. Should a neurologic deficit occur or postoperative retinal artery pressures fall, occlusion at the vascular site must be assumed. Accordingly, this patient should be returned to the operative suite with operative angiography followed by reopening of the endarterectomy and evacuation of the clot with subsequent restoration of flow. If an embolus has proceeded into the middle cerebral artery, a serious catastrophe has occurred. Immediate embolectomy or superficial temporal–middle cerebral artery bypass should be done to insure hemisphere perfusion.

Other complications include injuries to the hypoglossal and vagus nerves and mandibular branches of the facial nerve. Occasionally, the superior laryngeal or recurrent laryngeal nerve may be damaged.

ATHEROSCLEROTIC LESIONS OF THE VERTEBRAL ARTERY[3, 4, 13, 20, 29]

The vertebral artery has numerous collateral pathways through its radicular branches and communications with the ascending branches of the thyrocervical trunk and the external carotid artery. Therefore, vertebral artery occlusion and stenosis, particularly in its proximal portion, are usually not indications for surgical repair. The proven benefit of vertebral endarterectomy for high grade stenosis at its origin, particularly with the opposite vertebral artery being normal, is unknown. However, many surgeons routinely perform vertebral endarterectomy. In the presence of an occluded or absent vertebral artery with the remaining vessel being highly stenotic at its origin, surgical repair may occasionally be indicated. This is particularly true when

collateral vessels cannot be visualized, and communication between the anterior and posterior circle of Willis is absent. The vertebral artery may be compressed by muscular bands in its proximal portion. Surgical management includes the same medical considerations as well as preoperative and operative management described for carotid endarterectomy. The repair is effected by an incision at the base of the neck extending above the clavicle to expose the vertebral artery at the origin from the subclavian artery. After the patient receives heparin, the subclavian artery is occluded proximally and distally to the vertebral as well as occlusion of the internal mammary and thyrocervical trunk. The subclavian artery is opened, and an endarterectomy is done of the stenosis at the origin of the vertebral artery. Some surgeons prefer section of the vertebral artery with an end-to-side anastomosis of the vertebral artery to the common carotid artery. Whereas the patency rate after carotid endarterectomy is extremely high, the rate after vertebral endarterectomy is unknown.

The subclavian artery steal syndrome may occur on the right or the left side but is much more common on the left. This syndrome is due to a high grade stenosis or thrombosis of the proximal subclavian artery, provoking a reversal of flow in the vertebral artery supply to the distal subclavian and upper extremity. This syndrome rarely, if ever, leads to cerebral infarction but can produce symptoms of basilar insufficiency as well as exercise claudication in the upper limb. The lesion can be bypassed by instilling a vein or a dacron graft from the proximal common carotid artery into the subclavian artery.

UNUSUAL CERVICAL VASCULAR OCCLUSIVE LESIONS[23, 26]

Occasionally, the common carotid artery may be occluded by atherosclerotic plaque or spontaneous dissection. If the patient is symptomatic, careful angiography with delayed films determine whether or not the carotid bifurcation and the internal carotid artery are still patent. If they are, a bypass graft from the subclavian artery to the distal internal carotid artery can be effected. If a significant common carotid artery stump remains, at times the thrombosed section of the common carotid artery can be resected with an installation of an appropriate graft reconstituting flow.

Since the external carotid artery through its branches is a major collateral source of blood supply to the cerebral hemisphere in the presence of carotid thrombosis, an external carotid stenosis may produce cerebral insufficiency when the internal carotid artery has been previously thrombosed. External carotid endarterectomy may be required to insure adequate collateralization. This procedure is done in the same manner as carotid endarterectomy, but, since the plaque in the external carotid may extend into the branches or be difficult to remove, routine angioplasty is recommended.

EXTRACRANIAL/INTRACRANIAL BYPASS PROCEDURES[13, 20-22, 28, 29, 35, 36]

Since Donaghy and Yasargil developed superficial temporal artery to middle cerebral artery bypass anastomosis, it has become feasible to use not only the superficial temporal artery but the occipital artery to effect extracranial/intracranial microsurgical anastomoses. The efficacy of this procedure is presently being determined by an international cooperative study. Its superiority over the best available medical therapy has not been proven, but the procedure holds great promise. Microsurgical techniques are widely available with appropriate instrumentation and most neurosurgeons are becoming very competent and familiar with the procedure. The immediate patency rate of these anastomoses in the hands of experienced surgeons is 90 per cent. The long-term patency rate of arterial bypass surgery is undetermined, but many cases have been reported patent after several years, and significant enlargement of these anastomotic channels has been demonstrated. Indeed, many cases have been demonstrated with the anastomotic vessel responsible for the entire blood supply of the affected hemisphere. The morbidity and mortality of the procedure are quite low, being generally under 3 per cent for the mortality rate with a combined morbidity-mortality rate less than 6 per cent. Most of the clinical experience has dealt with anastomosis of the superficial temporal artery to a superficial cortical branch of the middle cerebral artery.[21, 22, 28, 35, 36] Less experience but successful cases of, anastomoses of the occipital artery to the middle cerebral artery as well as the posterior inferior cerebellar artery have been reported.[4, 13, 29] Rare cases of anastomoses between the superficial temporal or occipital artery and the superior cerebellar artery have been done. Some surgeons have anastomosed the occipital artery to cortical arteries of the cerebellar hemisphere. The favored branch anastomotic sites of the middle cerebral artery have been determined, but the cerebellar cortical arteries do not have consistent sites favorable to anastomosis. Indications for superficial temporal-middle cerebral artery anastomoses are as follows:

Symptomatic middle cerebral artery stenosis or thrombosis.
Intracranial carotid stenosis, symptomatic.
Carotid thrombosis with transient ischemic events.
Intracranial aneurysms of the carotid and middle cerebral arteries that require sacrifice of the vessel of origin to occlude the aneurysm.
Selected cases where the internal carotid artery must be sacrificed or is occluded by trauma.
Bilateral carotid artery occlusion with ischemic events.[21, 28, 35, 36]

Indications for occipital-posterior inferior cerebellar artery anastomoses are as follows:

Bilateral vertebral thrombosis, symptomatic.
Severe vertebral stenosis proximal to the posterior inferior cerebellar artery but not at the vertebral origin.[4, 13, 29]

Superior cerebellar anastomosis to the basilar artery is indicated when stenosis or occlusion occurs in the proximal basilar artery with persistent ischemic events.

Surgical Technique and Considerations[13, 21, 28, 29, 35, 36]

The medical evaluation and arteriographic studies are similar to those described under carotid endarterectomy. The surgeon must have excellent studies of the stenotic vessel and the collateral arterial supply to the hemisphere. The surgical technique requires considerable practice in the use of the operating microscope and in microvascular suturing. A specially trained microsurgical nurse and operating team are essential. Appropriate instruments for microsurgery are mandatory. Most of the anastomoses are done with 9–0 or 10–0 monofilament nylon suture with special needles; such as the BV-6 or the BV-5 needle (Ethicon). Interrupted suture technique is recommended, although some surgeons use a running suture.

The patient is placed supine on the operating table using endotracheal anesthesia with halothane, nitrous oxide, and oxygen. Blood pressure is carefully maintained, but induced hypertension is not required as it may be for cervical carotid surgery. The patient's head is turned to the side opposite the anastomosis and then, either through a curvilinear or horizontal suture, the largest branch of the superficial temporal artery is dissected free for sufficient distance to allow wide mobilization. The vasovasorum and surrounding tissue of the artery are maintained to insure good arterial supply to the graft.

Through a vertical incision in line with the external auditory canal and centered 6 to 8 cm above the external auditory canal, the underlying temporal bone and inferior parietal bone are exposed. A circular trephine craniotomy approximately 4 cm in diameter is done. This site insures ready access to the angular artery or the posterior temporal artery which are two of the cortical vessels that are usually 1 mm in diameter. To serve as a satisfactory graft, the superficial temporal artery should be at least 1 mm in external diameter.

The dura is opened, and a satisfactory cortical branch is identified. This vessel is freed of the surrounding arachnoid and, subsequently, isolated between two micro clips. The cortical branches of this vessel may require coagulation and division but should be preserved, if possible, to avoid local infarction. The superficial temporal artery is ligated and divided, and the distal end to be anastomosed is carefully freed of adventitia over a distance of not more than a centimeter. The end is usually sectioned obliquely and, subsequently, fish-mouthed to allow a wide area of suture.

The cortical vessel is opened with a linear arteriotomy about 4 mm in length, and a careful end-to-side anastomosis with 14 to 18 interrupted microsutures is done. Prior to final suturing, the vessels are flushed, and the anastomosis completed. The superficial temporal artery during the anastomosis is occluded with a small aneurysmal clip. Heparinization is not required. The dura is loosely approximated and the bone flap fashioned to prevent compromise of the anastomotic site. The temporalis and remaining wound are closed. The patient is al-

lowed to waken and carefully monitored as described under the procedure for carotid endarterectomy.

The patient is allowed to ambulate the next day and is usually discharged within 5 to 6 days. Postoperatively, the presence of a bruit over the anastomotic site confirms patency. Postoperative arteriography can be added to insure that the vessel is patent, and, if this is done, it probably should be delayed for at least one month. In view of the underlying risk factors of patients with cerebral occlusive disease, the patient must have careful medical management of risk factors and should be committed to long-term platelet-inhibiting drugs.

Complications

The complications[13, 21, 35, 36] of this procedure include graft thrombosis, the development of hemorrhagic infarction or intracerebral hematoma, subdural hematoma, and local scalp necrosis. Meticulous attention to operative technique minimizes these complications but reoperation for re-establishment of flow and/or evacuation of hematoma is occasionally required. Scalp necrosis is minimal. Upwards of 10 per cent of patients, particularly with operations on the dominant hemisphere, may have a transient neurologic deficit resulting from the cortical vessel occlusion. Rarely, persistent neurologic deficits are created. However, for the most part, the procedure is amazingly well-tolerated. The incidence of postoperative seizures is less than 1 per cent.

When the superficial temporal artery is absent or very small, the occipital artery can be used to effect the same type of anastomosis. This requires greater dissection and a longer incision, but, otherwise, the technique is identical.

The occipital-cerebellar artery anastomoses are more time consuming and difficult. The procedure is performed with the patient in the prone or sitting position, with the head held in the Mayfield head holder. A horseshoe occipital incision is made unilaterally, and the occipital artery is dissected from its muscle tunnel from the mastoid groove distally. Its adventitia is preserved. The artery is occluded with a small aneurysmal clip. Subsequently, an occipital craniectomy is made extending across the mid-line and the dura opened to expose the inferior loop of the posterior inferior cerebellar artery. Occasionally, if a large cerebellar cortical artery is present, this may be used for the anastomotic site. The posterior inferior cerebellar artery loop is isolated between microclips, and a linear arteriotomy approximately 4 mm in length is made, and the occipital artery is anastomosed to the posterior inferior cerebellar artery in a technique identical to the superficial temporal anastomosis. The dura is closed loosely with subsequent wound closure. The superior cerebellar anastomosis requires a temporal craniotomy with anastomosis transtentorially to the available superior cerebellar artery.

The future of microvascular anastomoses appears fruitful. However, until the procedure is well established and the criteria for the procedure clearly determined, it remains innovative and unproven for

most occlusive lesions. However, data have been reported indicating excellent results in preventing transient ischemic attacks as well as a trend indicating that strokes in the operated hemisphere are reduced. The benefit of the procedure in certain large aneurysms has been established.[28] This branch anastomosis can support good cerebral function and blood supply even in the face of sacrifice of the proximal middle cerebral artery.

SUMMARY

The role of surgery in preventing transient ischemic attacks and stroke in certain occlusive vascular lesions is well-established. This is well-established when carotid endarterectomy for carotid stenosis with transient ischemic attacks is used. The overall surgical results are best achieved by the frequent performance of the procedure and meticulous attention to technical as well as medical features of this group of patients at risk. Continuing medical care of these patients is essential. The long-term mortality rate is augmented by the high incidence of myocardial infarctions. Complete cardiac evaluation and good medical care, at the time the patient is initially treated, should subsequently minimize this event.

Although the microvascular bypass procedures are technically feasible and associated with a low morbidity and mortality rate, their exact role in the medical management of patients with intracranial occlusive lesions is unproven. However, the procedure offers great promise and an exciting future for neurosurgery in stroke therapy.

REFERENCES

1. Barnett, H. J. M., McDonald, J. W. D., and Sackett, D. L. A.: Aspirin — Effective in males threatened with stroke. (Editorial.) Stroke, *9*(4):295–298, July-August 1978.
2. Canadian Cooperative Study Group: A randomized trial of aspirin and sulfinpyrazone in threatened Stroke. New Engl. J. Med., *299*(2):53–59, July 13, 1978.
3. Cartlidge, N. E. F., Whisnant, J. P., and Elveback, L. R.: Carotid and vertebral-basilar transient cerebral ischemic attacks. Mayo Clin. Proc., 52:117–120, Feb. 1977.
4. Corkill, G., French, B. N., Michas, C., et al.: External carotid-vertebral artery anastomosis for vertebrobasilar insufficiency. Surg. Neurol., 7:109–115, March 1977.
5. David, T. E., Humphries, A. W., Young, J. R., et al.: A correlation of neck bruits and arteriosclerotic carotid arteries. Arch. Surg., *107*:729–731, Nov. 1973.
6. Javid, H., Ostermiller, W. E., Hengesh, J. W., et al.: Natural history of carotid bifurcation atheroma. Surgery, 67(1):80–86, Jan. 1970.
7. Eisenberg, R. L., Nemzek, W. R., Moore, W. S.: Relationship of transient ischemic attacks and angiographically demonstrable lesions of carotid artery. Stroke, *8*(4):483–486, July-August 1977.
8. Evans, W. E., and Cooperman, M.: The significance of asymptomatic unilateral carotid bruits in preoperative patients. Surgery, *24*(5):521–522, May 1978.
9. Fields, W. S.: The asymptomatic carotid bruit — Operate or not? Stroke, *9*(3):269–271, May-June 1978.
10. Fields, W. S., Lemak, N. A., Frankowski, R. F., et al.: Controlled trial of aspirin in cerebral ischemia. Stroke, *8*(3):301–314, May-June 1977.
11. Genton, E., Barnett, H. J. M., Fields, W. S.,: XIV. Cerebral ischemia: The role of thrombosis and of antithrombotic therapy. Stroke, *8*(1):150–175, January-February 1977.

12. Humphries, A. W., Young, J. R., Santilli, P. H., et al.: Unoperated, asymptomatic significant internal carotid artery stenosis: A review of 182 instances. Surgery, *80*(6):695–698, December 1976.
13. Khodadad, G., Singh, R. S., and Olinger, C. P.: Possible prevention of brain stem stroke by microvascular anastomosis in the vertebrobasilar system. Stroke, *8*(3):316–321, May-June 1977.
14. Kartchner, M. M., and McRae, L. P.: Noninvasive evaluation and management of the "asymptomatic" carotid bruit. Surgery, *82*(6):840–847, Dec. 1977.
15. Kurtzke, J. F., and Kurland, L. T.: Epidemiology of cerebrovascular disease. *In* Cerebrovascular Survey Report. Subcommittee on Cerebrovascular Disease. NINDS p. 163, 1970.
16. Lefrak, E. A., and Guinn, G. A.: Prophylactic carotid artery surgery in patients requiring a second operation. Southern Med. J., *67*(2):185–189, Feb. 1974.
17. Marshall, J., and Meadows, S.: The natural history of amaurosis fugax. Brain, *91*:419–434, 1968.
18. Moore, W. S., Malone, J. M., Boren, C., et al.: Asymptomatic ulcerative lesions of the carotid artery — Natural history and effect of surgical therapy compared. Stroke, *10*(1):96, Jan.-Feb. 1979.
19. Mungas, J. E., and Baker, W. H.: Amaurosis Fugax. Stroke, *8*(2):232–235, March-April 1977.
20. McNamara, J. O., Heyman, A., Silver, D., et al.: The value of carotid endarterectomy in treating transient cerebral ischemia of the posterior circulation. Neurology, *27*:682–684, July 1977.
21. Popp, A. J., Chater, N.: Extracranial-to-intracranial vascular anastomosis for occlusive cerebrovascular disease: Experience in 110 patients. Surgery, *82*(5):648–654, Nov. 1977.
22. Robertson, J. T.: Presidential Address: A neurosurgical approach to the therapy of extracranial occlusive disease. Clin. Neurosurg., *23*:1–11, 1976.
23. Robertson, J. T., and Auer, N. J.: Extracranial occlusive disease of the carotid artery. *In* Youmans, J. R., ed.: Textbook of Neurological Surgery. Philadelphia, W. B. saunders Co., in press.
24. Rodvien, R., and Mielke, C. H.: Platelet and antiplatelet agents in strokes. Stroke, *9*(4):403–405, July-August 1978.
25. Rollinson, R. D., and Toole, J. F.: Management of concomitant, symptomatic surgical lesions of the coronary and carotid arteries. Surg. Neurol., *11*:70–72, Jan. 1979.
26. Roome, N. S., and Aberfeld, D. C.: Spontaneous dissecting aneurysm of the internal carotid artery. Arch. Neurol., *34*:251–252, April 1977.
27. Sandok, B. A.: Noninvasive techniques for diagnosis of carotid artery disease. Stroke, *9*(5):427–429, Sept. — Oct. 1978.
28. Sundt, T. M., Siekert, R. G., Piepgras, D. G., et al.: Bypass surgery for vascular disease of the carotid system. Mayo Clin. Proc., *51*:677–692, November 1976.
29. Sundt, T. M., Whisnant, J. P., Piepgras, D. G., et al.: Intracranial bypass grafts for vertebral-basilar ischemia. Mayo Clin. Proc., *53*:12–18, 1978.
30. Swanson, P. D., Calanchini, P. R., Dyken, M. L., et al.: A cooperative study of hospital frequency and character of transient ischemic attacks. J.A.M.A., *237*(20):2202–2206, May 16, 1977.
31. Thompson, J. E., Patman, R. D., and Persson, A. V.: Management of asymptomatic carotid bruits. American Surgeon, *42*(2):77–80, Feb. 1976.
32. Treiman, R. L., Foran, R. F., Shore, E. H., et al.: Carotid bruit significance in patients undergoing an abdominal aortic operation. Arch. Surg., *106*:803–805, June 1973.
33. Vital statistics of the United States: Mortality. Dept. of Health Education and Welfare, U.S. Public Health Service, National Vital Statistics Division, Washington, D.C., 1964.
34. Wolf, P. A., Kannel, W. B., Gordon, T., et al.: Asymptomatic carotid bruit and risk of stroke: The Framingham Study. Stroke, *10*(1):96, Jan.–Feb., 1979.
35. Yasargil, M. G. L., Experimental small vessel surgery in dog including patching and grafting of cerebral vessels and the formation of functional extra-intracranial shunts. *In* Donaghy, R. M. P., and Yasargil, M. G., eds.: Microvascular Surgery. St. Louis, Missouri, C. V. Mosby Co., 1967. pp. 87–102.
36. Yasargil, M. G., and Yonekawa, Y.: Results of microsurgical extra-intracranial arterial bypass in the treatment of cerebral ischemia. Neurosurgery, *1*(1):22–24, July-August, 1977.

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Management of Intracranial Aneurysm

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Ruptured intracranial aneurysm is the most common cause of subarachnoid hemorrhage. Such intracranial bleeding, particularly recurrent bleeding, often leads to serious neurologic disability or death. To prevent these catastrophes, obliteration of aneurysms is the logical approach. Recent advances in neurosurgical technique, especially progress in microsurgery, have made aneurysm obliteration both effective and safe. In this setting, prompt diagnosis of subarachnoid hemorrhage has become pivotal for optimum results. Management of the complications of subarachnoid hemorrhage, including cerebrovascular vasospasm, remains a major problem in this field.

Prevalence

Cerebral aneurysm and subarachnoid hemorrhage are common problems. Estimation of the actual prevalence of ruptured intracranial aneurysm is limited by hospital, autopsy, and population biases. The overall prevalence of cerebral aneurysm in the general population is estimated to be 9.6 per 100 thousand.[41] Of all maternal deaths in Minnesota from 1950 to 1973, 4.4 per cent were due to ruptured intracranial aneurysm.[3] Subarachnoid hemorrhage represents about 8 per cent of all cases of cerebrovascular disease.[32] These figures stress the great prevalence of cerebral aneurysm, an important lesion because it is treatable.

The prevalence of aneurysm in the population is highly correlated with age; the peak incidence is in the sixth decade of life, and substantial numbers of aneurysms are found in all decades after the second. Aneurysms are rare in childhood and adolescence.[18, 42] Initial morbidity and the rate of cerebral infarction are less severe in children, and the recovery from neurologic deficit is more complete.[42, 50]

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A slight tendency toward female preponderance is characteristic. There is risk to a mother harboring intracranial aneurysm during labor and delivery;[3] craniotomy is sometimes recommended for expectant mothers with intracranial aneurysm. Several authors have reported a familial incidence of aneurysm.[21, 25, 47] The onset of symptoms in familial cases appears to be much earlier than in nonfamilial cases. In asymptomatic members of a family with more than one case of intracranial aneurysm, angiographic evaluation is probably warranted.

The frequency of subarachnoid hemorrhage from demonstrated intracranial aneurysm is difficult to ascertain. However, recent reports indicate that patients with subarachnoid hemorrhage from aneurysm suffer another hemorrhage at a rate of 3 per cent per year with a fatality rate of 2 per cent per year.[26, 69] Limited data suggest similar rates of re-bleeding and death related to previously unruptured aneurysms. These important data emphasize the serious threat of morbidity and mortality from intracranial aneurysm.

ETIOLOGY

Several etiologies have been suggested for the usual variety of intracranial aneurysms, but no single mechanism has been firmly established. The occasional occurrence of cerebral aneurysm with congenital disorders, such as coarctation of the aorta and polycystic kidney disease, has lent some credence to the concept of a developmental mechanism. The familial occurrence of aneurysms also gives support to a developmental etiology. On the other hand, the very low prevalence of cerebral aneurysm in infancy and childhood indicates that the lesions themselves are not congenital; at best, a predisposition toward later aneurysm formation might be present at birth.

Other authors have advocated a degenerative or inflammatory mechanism. The ultrastructural study of Stehbens, which showed abundant destruction of elastica in aneurysmal walls, gives some support to this theory.[37] Other reports of liposome-like granules in close association with the disintegrating elastica suggest enzymatic destruction by leukocyte granules.[7]

Traumatic aneurysms, caused by head injury, are an infrequent cause of subarachnoid hemorrhage. These lesions often bleed within three weeks of the original trauma. Because the aneurysms tend to change in shape and size, serial angiograms should be performed before surgical obliteration is carried out.[4]

Mycotic aneurysms occasionally arise as a sequel to bacterial endocarditis, and typically occur in distal branches of the cerebral arterial tree. Since many of these lesions disappear, surgery is recommended only if the aneurysm persists or enlarges on cerebral angiography.[5]

Atrial myxoma is occasionally associated with multiple intracranial aneurysms, which result from tumor emboli that invade and destroy the arterial wall.[10]

PATHOLOGY

Intracranial aneurysms arise within specific sites in the cerebral circulation (Fig. 1). Approximately 85 per cent of them occur in the anterior circulation (internal carotid arteries and branches). Most aneurysms of the anterior circulation are found at the anterior communicating artery, the internal carotid artery, and the middle cerebral artery, particularly at its bifurcation. Aneurysms arising on the distal branches of these vessels are distinctly uncommon (see mycotic aneurysms). Drake[12] has stressed the occurrence of aneurysms in the posterior circulation (vertebral or basilar arteries and branches). These lesions, which are now treatable by modern microsurgery, are most common at the apex of the basilar artery and at the take-off of the posterior-inferior cerebellar arteries. The incidence of multiple intracranial aneurysms may be as high as 15 per cent, particularly in mirror locations, such as bilateral middle cerebral aneurysms. For this reason, complete antiography should be performed in every patient known to harbor a single lesion.

Gross examination of aneurysms indicates that these lesions generally arise from bifurcations of major proximal intracranial arteries of (Fig. 1). They sprout like buds at branch points. Most of these lesions have a definable neck for surgical clipping. Many lesions are multilobular, and during surgical therapy or at post-mortem examination, remarkable thinning of their walls may be observed at the area of bleeding.

Some aneurysms grow to a large size; diameters of 10 cm are seen on occasion. Thickening, thrombosis, and calcification of the wall are often seen.

Histopathologic examination reveals thinning of the arterial wall with absence of internal elastic lamina. The location of this attenua-

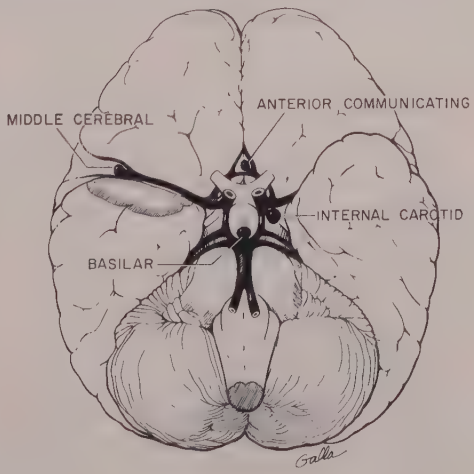

Figure 1. *Locations of intracranial aneurysms.* The commonest sites for aneurysms are: (1) anterior communicating artery (may be associated with confusion or memory loss); (2) internal carotid artery (possible third cranial nerve palsy); (3) middle cerebral artery (possible hemiparesis or aphasia); (4) basilar artery or vertebral artery (possible dysfunction of brain stem or cranial nerves).

Table 1. *Complications of Subarachnoid Hemorrhage*

COMPLICATIONS	CLINICAL FEATURES	DIAGNOSTIC TESTS	THERAPY
Increased intracranial pressure	Headache, decreased alertness	Lumbar puncture,* ventricular puncture, subarachnoid screw	Steroids, mannitol
Intracerebral hematoma	Immediate focal deficit	CT	Steroids, mannitol, consider evacuation
Vasospasm-infarction	Delayed focal deficit	Angiography. CT may show ischemia; cerebral blood flow	Volume replacement, blood pressure maintenance. (? drugs)
Seizures	Focal motor seizures	EEG	Anticonvulsants
Hydrocephalus	Decreased alertness-increased deficit	CT (and lumbar puncture)	Ventricular drainage or ventriculoatrial shunt
Recurrent subarachnoid hemorrhage	Recurrent headache or deterioration	CT (and lumbar puncture)	Aneurysm obliteration
Hypothalamic disturbance: SIADH	Neurologic deterioration	Serum electrolytes	Fluid restriction
Cardiac abnormalities	Arryhthmia, myocardial infarct	EKG, cardiac enzymes	Therapy of arryhthmia therapy of myocardial infarction
Hypertension	Increased blood pressure		Antihypertensive medication

*Should be done with caution.

tion corresponds to medial defects which appear at branch points in normal arteries. Cerebral arteries are particularly vulnerable to the mechanical effects of pulse pressure, as they have little external elastic lamina and no extrinsic tissue support. Normal cerebral arteries have less external elastic lamina than peripheral arteries.

PATHOPHYSIOLOGY

A summary of pathophysiologic details is presented in Figure 2 and Table 1. *Growth of aneurysms* has been documented by serial angiography. In 67 patients with 82 intracranial aneurysms, nearly 70 per cent of the lesions enlarged with time.[1] Because of the propensity of aneurysms to enlage, some clinicians suggest that small aneurysms (less than 5 mm) should be followed with arteriographic examination at 1 year intervals. The mechanism of aneurysmal growth has not been clearly established, but Suzuki and Ohara[61] have suggested a plausible theory. Under certain unspecific conditions, the water hammer effect of the pulse causes ballooning of the normal gap in internal elastic lamina found at an arterial bifurcation. Proliferation of adventitia thickens the neck of the aneurysm, while the fundus, poorly bolstered by adventitia, expands in response to transmural pulsatile forces.

Aneurysmal rupture may lead to minor or catastrophic subarachnoid hemorrhage (Fig. 2). The pressure of the pulse finally pierces a tiny hole in the aneurysm fundus. Bleeding is probably very brief in most instances, leading to headache, nausea, vomiting, and, less frequently, loss of consciousness. In some cases, massive hemorrhage quickly fills the basal cisterns and ventricular system, leading to coma and death. More commonly, bleeding is stopped by tissue pressure and the formation of a fibrin-platelet plug at the site of rupture. This seal may be difficult to find even a few hours after aneurysmal bleeding.

Increased intracranial pressure is a common sequel of acute subarachnoid bleeding from intracranial aneurysms. Hayashi et al.[22] showed that impaired consciousness in patients with subarachnoid hemorrhage is related to increased intracranial pressure rather than cerebral vasospasm. Raised intracranial pressure may act to retard recurrent subarachnoid hemorrhage; in cases of ruptured aneurysm monitored for intracranial pressure, recurrent hemorrhage tended to occur as the intracranial pressure returned toward normal.[39]

Hypothalamic irritation[27, 67] by subarachnoid bleeding may lead to a variety of systemic abnormalities. (1) *Electrolyte imbalance* is common after subarachnoid hemorrhage, and in many cases is shown to be the result of inappropriate secretion of antidiuretic hormone. (2) *Cardiac abnormalities*[9, 20, 66] are sometimes observed, including cardiac arrhythmias. In some cases, electrocardiographic changes may indicate actual myocardial infarction. More commonly, electrocardiographic changes are transient and unaccompanied by cardiac enzyme

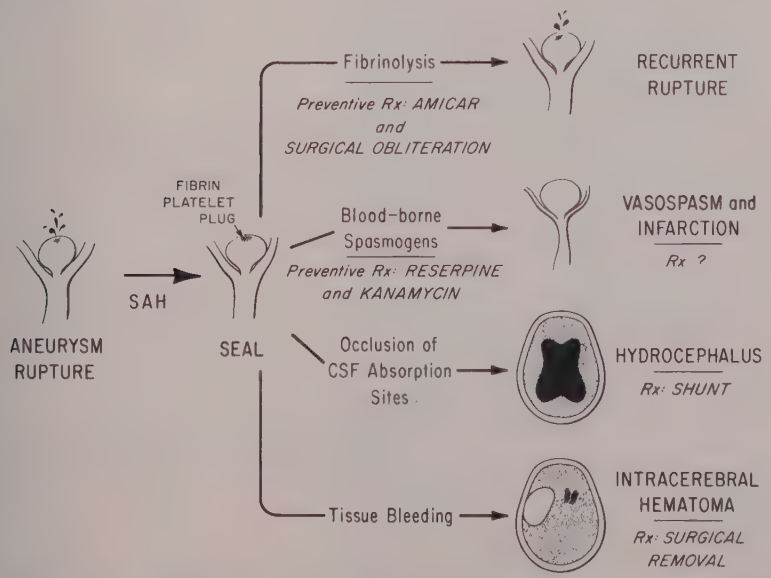

Figure 2. *Pathophysiology of subarachnoid hemorrhage.* Major complications are shown with potential therapies.

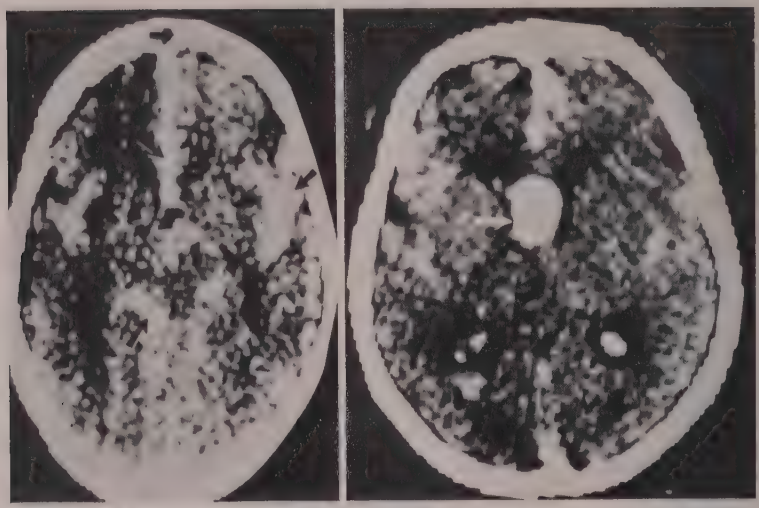

Figure 3. Computed tomography may demonstrate (left) subarachnoid blood in unenhanced scan (arrows) and (right) anterior communicating aneurysm filling on enhanced scan (arrow).

abnormalities. Q waves, elevated ST segments, and ST- and T-wave changes are commonly observed. (3) *Hormonal abnormalities*[9, 40] have been observed after subarachnoid hemorrhage. The most common are abnormal levels of hydroxycorticosteroids, abnormal dexamethasone suppression test, and disturbance of the normal circadian secretion of steroid hormones.

Neurologic Complications

Neurological complications are common following subarachnoid hemorrhage (Fig. 2 and Table 1). (1) Intracerebral hematoma may result from prolonged subarachnoid hemorrhage. In such cases immediate focal deficit related to the mass is common, and surgical evacuation may be the treatment of choice. (2) Seizures are not uncommon sequels to subarachnoid bleeding which irritates the cortex. (3) Communicating hydrocephalus often occurs after subarachnoid hemorrhage, particularly when bleeding is severe. Delayed deterioration may accompany this complication which is best diagnosed by CT scan and lumbar puncture. Ventriculoatrial shunting may be curative. (4) Recurrent subarachnoid hemorrhage is the most lethal and feared complication of subarachnoid hemorrhage from ruptured intracranial aneurysm. Recurrent headache may herald profound deterioration. Surgical obliteration of the aneurysm is the best prophylactic treatment.

Cerebrovascular Vasospasm

Cerebrovascular vasospasm with cerebral infarction is a poorly understood and frequent complication of subarachnoid hemorrhage[11, 33, 63] (Figs. 2 and 3). Vasospasm is defined as radiographically

measurable constriction of cerebral arteries after ruptured aneurysm.[2] The arterial constriction leads to cerebral ischemia and infarction with attendant delayed ischemic deficit.[11] Among 50 patients with subarachnoid hemorrhage, only those with severe arterial constriction developed delayed ischemic deficits.[14] Cerebral symptoms were not present in patients with a vessel diameter greater than 1 mm.

Vasospasm is a common problem. More than half the patients with ruptured intracranial aneurysm have discernible cerebral vasospasm; of these, 20 to 36 per cent will develop ischemia or infarction.[44, 60] The clinical syndrome of delayed ischemic deficit is marked by neurologic deterioration occurring from 4 to 16 days after initial hemorrhage, most commonly about the ninth or tenth day. Minor symptoms of drowsiness are commonly followed by hemiparesis or hemiplegia, aphasia or other focal neurologic abnormalities. In the most severe cases, increased intracranial pressure and death may result. For the less stricken, gradual recovery may begin within a few days and in some cases may be quite complete.

Diagnosis of cerebral vasospasm cannot rest on clinical criteria. Headache and neurologic deterioration, including focal neurologic signs, may stem from inappropriate secretion of antidiuretic hormone, dehydration, drug intoxication, rebleeding, or hydrocephalus. Definitive diagnosis of vasospasm rests on angiographic demonstration of severely constricted arteries.

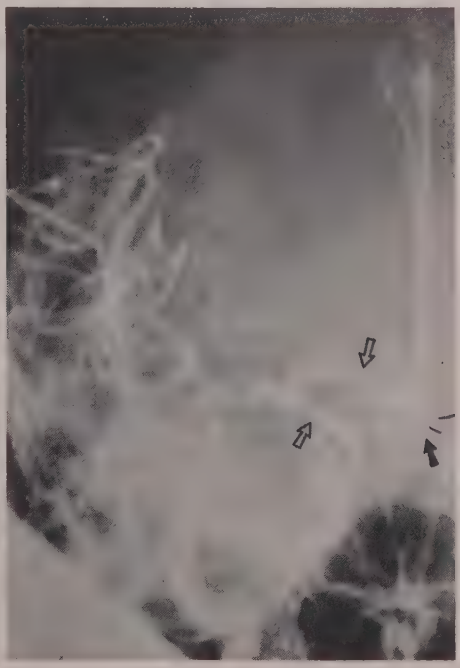

Figure 4. *Cerebral angiography* demonstrates an anterior communicating aneurysm (closed arrow) and cerebral vasospasm (open arrows).

Two general mechanisms seem important in the evolution of cerebral vasospasm. (1) Vasoconstrictive substances are released by activated platelets, cerebral tissue or red blood cells. Among the substances thought to be important are serotonin, prostaglandins and thromboxanes. In addition, the decomposing products of hemolyzing blood, including protein and hemoglobin catabolites, may possibly be vasoactive agents. (2) Hypothalamic dysfunction may result in the generalized discharge of catecholamines which in turn constrict cerebral arteries, particularly those irritated by subarachnoid blood and unable to deactivate circulating catecholamines.[67] If regional cerebral blood flow is not reduced below a critical threshold, constriction of the large conducting vessels may produce no symptoms at all. If the constriction is severe and blood flow falls below the critical threshold, there may be symptomatic cerebral ischemia and perhaps infarction.

Vasospasm causes a variety of cerebrovascular sequelae. In a recent report, regional cerebral blood volume, regional cerebral blood flow, and regional cerebral oxygen utilization were studied in 3 patients during angiography for evaluation of subarachnoid hemorrhage.[19] Cerebral blood flow and cerebral oxygen utilization were significantly decreased whether or not vasospasm was present while marked depression of cerebral blood flow and cerebral oxygen utilization was observed in patients with severe cerebral vasospasm. A significant increase in cerebral blood volume was seen in patients with severe neurologic deficits associated with severe cerebral vasospasm.

CLINICAL PRESENTATION

Premonitory symptoms often suggest the presence of unruptured aneurysms.[29] Such premonitory features may precede rupture in as many as 60 per cent of patients, but their recognition is often quite difficult. Localized periorbital pain with third-nerve palsy indicates compression of the third nerve, generally by an internal carotid-posterior communicating artery aneurysm. This presentation, while not common, is of sufficient diagnostic accuracy as to warrant emergency angiography and (potentially) surgical intervention.[55] Headache with poor localization, nausea, back pain, lethargy, and photophobia may also be associated with intracranial aneurysm, but these symptoms are not specific or diagnostic.

Subarachnoid hemorrhage is the most frequent presentation of intracranial aneurysm. Fortunately, many episodes of subarachnoid bleeding are of a minor nature, with little or no resultant neurologic dysfunction. The most common symptom of such hemorrhage is headache. Patients usually describe the headache as the worst in their experience, usually of sudden onset, sometimes associated with brief loss of consciousness, nausea and vomiting, neck pain, back pain, photophobia, and generalized malaise. In many instances, the ictus of subarachnoid hemorrhage is related to physical effort, and a history of subarachnoid bleeding in relation to intercourse is not uncommon. In some cases "seizure" is the presenting complaint. These symptoms

may be accompanied by immediate transient neurologic deficits, including hemiparesis, aphasia, or third-nerve palsy. These deficits help the clinician to localize the site of bleeding; for example, a right hemiparesis with transient aphasia point to bleeding from the left middle cerebral or internal carotid arteries.

Immediate neurologic deficits persist in many patients. The generalized insult from bleeding may be expressed as acute confusion, fever, or hypertension. Pre-retinal hemorrhage, a distinctive fingerprint of subarachnoid bleeding, is frequently present. Some persistent deficits point to localized damage related to hemorrhage. One of the most frequent signs is the Babinski sign, which points to contralateral middle cerebral or internal carotid territory disease. This sign may be accompanied by a hemiparesis or dysphasia. A sixth-nerve palsy or other lower cranial-nerve dysfunction may suggest posterior fossa pathology, although an isolated sixth nerve palsy may simply reflect increased intracranial pressure. Acute confusion, memory disturbance, and personality change may result from an anterior communicating aneurysm with local damage to the inferior frontal lobe. Some patients with massive bleeding may quickly plunge into coma, never to recover.

Delayed complications of subarachnoid hemorrhage are frequent and their variety may baffle the clinician (Table 1, Fig. 2). The three most common causes of delayed neurologic deficit are vasospasm, hydrocephalus, and recurrent subarachnoid hemorrhage. Symptomatic vasospasm rarely, if ever, develops before the third day. Hydrocephalus generally decreases the level of alertness and may exacerbate focal neurologic deficit. Subarachnoid hemorrhage may recur with or without obvious headache. Generally, CT scanning and lumbar puncture, if done with caution, will identify recurrent subarachnoid hemorrhage or hydrocephalus. A strong suspicion of cerebral vasospasm is therefore confirmed by the process of elimination; cerebral angiography is required for direct confirmation.

Giant cerebral aneurysms may present as mass lesions. These lesions, arising most frequently from the middle cerebral and internal carotid arteries, may give rise to slow and progressive hemiparesis and dysphasia. Careful CT evaluation with and without contrast material may lead to the correct diagnosis.[33]

Ischemic deficit is an unusual sequel to cerebral aneurysm, and may be related to arterial occlusion with embolization from an aneurysmal sack partially filled with clot.

Grading or classifying patients with subarachnoid hemorrhage on the basis of clinical status is helpful in their management. The classification offered by Botterell,[6] as modified by Hunt,[24] has proved useful to many clinicians (Table 2). In general, patients in grades 1 and 2 are managed medically for about 10 days; operation is then indicated to prevent recurrent hemorrhage. Patients in grades 3 and 4 are allowed 3 to 4 weeks to stabilize before surgery. Moribund patients are not candidates for operation except for removal of life-threatening hematomas or shunts for hydrocephalus.

Table 2. *Classification of Patients with Subarachnoid Hemorrhage**

Grade 1	Conscious, with or without signs of blood in the subarachnoid space.
Grade 2	Mild drowsiness, headache, no neurologic deficit.
Grade 3	Drowsiness, confusion, focal neurologic deficit.
Grade 4	Stupor, moderate to severe neurologic deficit.
Grade 5	Coma, with moribund appearance.

*Modified from Botterell.[6]

EVALUATION

Computed Tomography

Computed tomography (CT) has revolutionized the investigation of subarachnoid hemorrhage [1, 33, 48] (Fig. 4). This scanning technique often makes the diagnosis of subarachnoid bleeding without the risks involved in lumbar puncture. The advantage of CT scanning is particularly appropriate in patients who may suffer from increased intracranial pressure, that is, patients in grades 3 to 5 with significant neurologic deficit. In such cases, CT should be performed as the initial diagnostic study to avoid the significant risk of transtentorial herniation following lumbar puncture.[11] CT without contrast enhancement may also document subarachnoid hemorrhage in patients in class 1 or 2 without significant neurologic deficit. In these patients, lumbar puncture is less risky and should be used to confirm the diagnosis of subarachnoid bleeding, which occasionally can be missed by CT scanning.[48] In some patients with multiple cerebral aneurysm or cerebral aneurysm and cerebral arteriovenous malformation, CT may specify which of the various lesions has actually bled. Computed tomography is also useful for the diagnosis of complications in subarachnoid hemorrhage, including intracerebral or intraventricular hematoma, hydrocephalus, and cerebral infarction. To permit the rapid diagnosis of these adverse developments, CT scanning should be performed on admission for all patients with subarachnoid hemorrhage and promptly after any deterioration.

The utilization of CT scanning permits accurate diagnosis of the etiology of subarachnoid hemorrhage in most patients. The location, form and distribution of hemorrhage, together with direct enhancement of the aneurysm itself, establishes the diagnosis of intracranial aneurysm. Similarly, cerebral arteriovenous malformations may be seen in unenhanced and, more commonly, in enhanced CT scans. The appearance of giant intracranial aneurysms, with enhanced residual lumen and unenhanced high density partial thrombosis, is particularly distinctive in CT depiction.[33] Computed tomography is the safest and most useful examination in the evaluation of patients with suspected subarachnoid hemorrhage.

Lumbar Puncture

Lumbar puncture still plays a role in the evaluation of subarachnoid hemorrhage. Particularly in cases of subarachnoid bleeding with-

out neurologic signs, sampling of the lumbar subarachnoid spinal fluid can be diagnostic and lead to appropriate management. The patient with sudden severe headache and a normal neurologic examination may require spinal puncture. This approach is particularly appropriate in hospitals where CT is not readily available. Lumbar puncture should be done carefully to avoid traumatic bleeding. To be sure that bloody CSF is not the result of a traumatic tap, a CSF sample should be centrifuged, as the breakdown of hemoglobin leads to xanthochromic supernatant within a few hours of subarachnoid bleeding. Occasionally, repeat lumbar puncture is required to document subarachnoid bleeding, as cisternal blood may take several hours to migrate to the lumbar subarachnoid space. Lumbar puncture should always be performed with caution, however, since transtentorial herniation could result in patients with increased intracranial pressure.

Radionuclide Studies

Radionuclide dynamic flow studies may indicate the presence of local diminution of flow which suggests deferral of surgical intervention.[28]

Angiography

Angiography remains the procedure of choice for the precise characterization of bleeding intracranial lesions (Fig. 3). Special views may be required to distinguish small aneurysms, to outline an aneurysmal neck, or to confirm a loop configuration. In most cases, angiography may be deferred until just before surgery, as vasospasm can be evaluated in close temporal relation to operation. This strategy of timing for angiography avoids immediate study on admission. A search for vasospasm is the other major indication for angiography; definite evidence of vasospasm can only be gained when narrowing of cerebral vessels is seen on angiographic investigation. Because extensive angiography may actually exacerbate cerebrovascular vasospasm, angiographic studies are usually terminated once vasospasm has been demonstrated. In some centers, angiotomography is used for the precise anatomic definition of the location and configuration of complicated aneurysms.[45]

Medical Evaluation

Medical evaluation is of special importance in patients with aneurysm. Frequently cardiac consultation is required because of cardiac stress that may result from deliberately induced hypotension during aneurysmal surgery. Electrocardiogram and chest film are routine. Bleeding parameters should be determined in all patients, including prothrombin time, partial thromboplastin time, and platelet count. Serum electrolytes and blood urea nitrogen are sampled as needed, as the syndrome of inappropriate antidiuretic hormone secretion is common. Non-invasive vascular evaluations of the lower extremities (plethysmography) may be used to screen for deep vein thrombosis, which may occur in patients treated with epsilon aminocaproic acid.

MEDICAL MANAGEMENT

Bedrest

Bedrest has traditionally been used to avoid recurrent subarachnoid hemorrhage.[38] "Aneurysm precautions" usually include a darkened quiet room, limited visitors, and avoidance of radio and television. Stool softeners are administered to avoid straining at stool, which can lead to recurrent subarachnoid bleeding. Sedatives are administered to avoid upset and consequent hypertension. Anticonvulsants, such as diphenylhydantoin, are administered to prevent seizures which could be harmful. In patients with neurologic deficit and increased intracranial pressure, corticosteroid therapy may be beneficial.

Antifibrinolytic Agents

Antifibrinolytic agents have provided a major advance in the medical management of ruptured aneurysm.[15, 34, 37] Since fibrinolysins in cerebrospinal fluid lyse the clot sealing the aneurysm leak, antifibrinolytic therapy is a logical approach to prevent the recurrent bleeding which commonly occurs in the first two weeks after the initial hemorrhage. Several studies indicate that the incidence of rebleeding is substantially diminished in patients who receive the antifibrinolytic agent, epsilon aminocaproic acid (EACA). In one study, the incidence of early rebleeding after administration of EACA and hypotensive therapy was 11.8 per cent.[44] The recommended dose of EACA is 30 to 36 gm a day, administered intravenously until surgery or for 21 days if surgery is not performed.[37] Some authors have recommended oral therapy.[49] The use of antifibrinolytic therapy, however, carries a risk of thrombotic complications, and some authorities recommend caution in its use.[56] More recently, successful results have been obtained with tranexamic acid;[17, 34, 64] confirmed rebleeding was 12 per cent in one group of patients treated with this agent. To prevent deep vein thrombosis in the lower extremities, intermittent pneumatic calf compression may be useful.

Antihypertensive Agents

Antihypertensive therapy is used in many centers to prevent recurrent bleeding, but there are conflicting reports about its efficacy. Slosberg[53, 54] recommends vigorous antihypertensive therapy (aiming for a systolic blood pressure of 80 to 90 mm Hg) and has reported good long-term results in a selected group of patients. However, it is possible that lowering the blood pressure to hypotensive levels is harmful to patients with ruptured aneurysms. We administer antihypertensive medication (hydralazine, propranolol) to achieve normal blood pressure. Occasionally, marked hypertension can be controlled only with intravenous agents, such as trimethaphan or nitroprusside.

Intracranial Pressure

Management of intracranial pressure may be guided by careful examination, CT scanning, and careful lumbar puncture. Devices that continuously monitor intracranial pressure are advocated by some, but

their contribution to survival remains unclear. If increased intracranial pressure is present, many clinicians use corticosteroid therapy, although clear-cut evidence of benefit is not available. Nornes has cautioned against the use of hyperosmolar agents (mannitol) because of possible rebleeding upon precipitous reduction of intracranial pressure.[39] However, the use of such agents in the rapidly deteriorating patient is generally accepted.

Cerebrovascular Vasospasm

Cerebrovascular vasospasm remains a difficult problem in management. A large number of experimental and clinical therapies have been used in the treatment of vasospasm. A recent review cited therapies that are now commonly used in clinical practice.[51]

Pressor agents have been used to increase systemic arterial pressure and perfusion through spastic cerebral vessels.[13] Kosnik and Hunt[30] have reported improvement in neurologic symptoms after sustained hypertension. Pressor agents produce tachyphylaxis, however; additional measures then must be taken, including administration of blood or fluids to expand blood volume.[16, 65]

Isoproterenol, an adrenergic drug which dilates vascular smooth muscle, has been given to patients with symptomatic vasospasm.[59] To counteract cardiac irritability, lidocaine is administered concurrently. Good to excellent responses were reported in 22 of 30 patients treated with this regimen.

Aminophylline combined with isoproterenol has been reported to be helpful.[16] Twelve patients were treated with infusion of these drugs, and 9 patients improved in one clinical series.

Reserpine and kanamycin reduce blood serotonin, an agent known to cause vasoconstriction. Prophylactic administration of these agents has been reported to diminish the incidence of delayed ischemic deficits particularly after operation.[72]

SURGICAL THERAPY

Dramatic advances in surgical technique have led to marked improvement in results, which were disappointing 10 years ago.[52] Most authorities now agree that microsurgical obliteration of aneurysms offers a safe and effective means of preventing dangerous recurrence of subarachnoid bleeding.

The development of microsurgical techniques is the most striking factor in the surgical therapy of aneurysms[70] (Fig. 5). In 1967, Donaghy and Yasargil showed that the operating microscope vastly improved visualization and lighting of tiny neural structures and arteries deep in the neurosurgical field. Subsequently, the complication rate of microsurgical aneurysm repair was markedly reduced in many centers.[12, 23, 31, 35, 60, 62, 70] In experienced hands, the complication rate for such intracranial surgery is now less than 5 per cent for good risk patients. In a recent report, Sundt and Whisant[60] found that, among 280 patients in good condition prior to aneurysm surgery, only 2 had poor

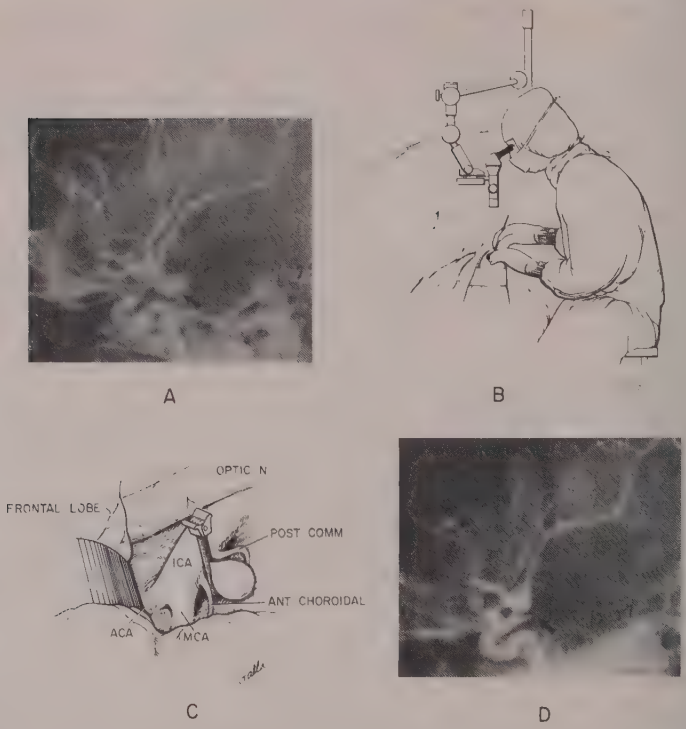

Figure 5. *Microsurgical clipping* of aneurysms is now safe and effective. A. Pre-operative angiogram shows internal carotid artery aneurysm (arrow). B. Sketch indicates surgeon and operating microscope during obliteration of aneurysm. C. Microsurgical field. The right frontal lobe is gently elevated from internal carotid aneurysm (ANR) which has been clipped. Note carefully preserved optic nerve and neighboring arteries. D. Post-operative angiogram shows non-filling of aneurysm and preserved normal arteries. Patient recovered fully.

results and 2 died. In 100 consecutive patients in good preoperative condition at the Massachusetts General Hospital, there were 2 deaths after aneurysm surgery. Given a high rate of recurrent bleeding (as high as 30 per cent in the first year), intracranial direct obliteration of aneurysms may be confidently recommended for most patients. The evidence for this view is highly suggestive, although no controlled study has yet been presented.

Details of microneurosurgical technique fall outside the scope of this paper; however, a brief overview may be helpful (Fig. 5). The most useful adjunct is the surgical operating microscope which permits sharp visualization under excellent illumination of small intracranial vascular and neural structures. In particular, minute perforating vessels may be identified and spared. A battery of microsurgical instruments has been developed for optimal obliteration of aneurysm. Three-point skeletal fixation with a head holder allows rigid positioning of the microsurgical field. Automatic self-retaining brain retractors

gently lift the brain 1 to 2 cm from the base of the skull, permitting excellent visualization of the circle of Willis without excessive retraction trauma. The bipolar coagulator allows precise, minimally traumatic hemostasis, even immediately adjacent to neural and vascular structures. A variety of microdissectors have been developed to permit delicate dissection of neurovascular structures, including aneurysms. A wide variety of aneurysmal clips, some ingeniously complex, are available for the obliteration of intracranial aneurysms. When clipping of an aneurysm is impossible, certain rapidly polymerizing tissue adhesives may invest the aneurysm with an impenetrable plastic coating. Should vasospasm occur intraoperatively, the topical application of papaverine to spastic vessels increases their diameter. Most surgeons perform angiography one to two weeks following surgery to ascertain position of the aneurysmal clip, which is repositioned if unsatisfactory obliteration is in evidence.

Neuroanesthesia provides another critically important modern adjunct for aneurysm surgery. By the use of corticosteroids, mannitol, and spinal drainage, it is now possible to provide a very slack brain for safe obliteration of aneurysms. Perhaps the most potent neuroanesthetic weapon is controlled hypotension, which permits extensive aneurysmal dissection and preparation impossible at normotension. At a mean pressure of 40 mm Hg, "the bomb is defused."[12]

In the days prior to microsurgery, direct attack on aneurysms was forbiddingly risky. Therefore, a number of indirect treatments were devised. In certain situations, particularly giant or inaccessible aneurysms, these approaches are still used. Carotid ligation gained popularity in the 1950's. Early experience indicated that common carotid ligation was safer than internal carotid ligation and might lead to thrombosis of aneurysms, particularly those of the intracranial internal carotid artery. More recently, internal carotid ligation has been recommended to thrombose certain internal carotid aneurysms which are inaccessible or of large size, with the adjunct of superficial temporal-middle cerebral bypass grafting to prevent ischemic complications. In some cases, bypass grafting permits the occlusion of other intracranial vessels, such as the middle cerebral artery trunk in cases of unapproachable middle cerebral aneurysm. A related approach to anterior communicating aneurysms is the tactic of proximal anterior cerebral artery clipping, which may diminish the distal intra-arterial pressure and lead to aneurysmal thrombosis, while collateral circulation sustains distal brain tissue. It must be noted however, that such proximal ("Hunterian") ligations sometimes fail to thrombose the distal aneurysm and may lead to ischemic complications.

Innovative alternative approaches to aneurysm surgery have been developed such as stereotactic obliteration of intracranial aneurysms and open introduction of fine thrombogenic wire into certain giant aneurysmal lesions. Stereotactic introduction of ferromagnetic particles into aneurysms, with local magnetic attraction to hold the thrombogenic particles within the aneurysmal lumen has been used. Other investigators have utilized angiographically controlled transvascular po-

sitioning of catheters within aneurysms and attempted thrombosis, either with detachable balloons or injected thrombogenic materials. These ingenious approaches await refinement.

The timing of surgery for obliteration of aneurysms remains controversial. For grade 1 and 2 patients, operation after 1 to 2 weeks of medical therapy is generally advocated. For patients in grade 3 and 4, surgery is generally deferred until recovery or at approximately 3 to 4 weeks after bleeding. During this time maximum recovery can occur, undisturbed by the trauma of surgery, however minimal. For patients in class 5, surgery is not recommended because of their moribund condition.

Some clinicians advocate early surgery to avoid the complications of recurrent bleeding and vasospasm. Results of early surgery in the era before microsurgery were discouraging, but recent reports from Japan[46] have suggested that good results can be obtained. At this time, the value of early aneurysm surgery remains controversial.

Timing of surgery for the patient in good neurologic condition with angiographic vasospasm presents a difficult problem. Most clinicians defer surgery for 2 weeks. After the two week interval, however, Drake has advocated prompt surgery for these cases, arguing that spasm at this time is no longer an ominous harbinger of postoperative disaster.

Emergency surgery is sometimes indicated for the complications of subarachnoid hemorrhage. For example, the patient with substantial focal deficit and intracerebral hematoma often requires emergency evacuation of the intracerebral hematoma. In most instances, the offending aneurysm can be clipped directly to avert subsequent subarachnoid hemorrhage. In some patients with minor hematoma and deficit, medical management may be elected as the initial step. In such cases, deterioration may demand emergency evacuation of the clot. Hydrocephalus is another complication which may force emergency surgery, which may be accomplished by temporary closed ventricular drainage or, in some cases, ventriculoatrial or ventriculoperitoneal shunting procedures. Spinal subarachnoid drainage may actually lead to clinical improvement and set the stage for definitive operation. Such clinical improvement may be related to increased cerebral perfusion pressure, achieved by decreasing intracranial pressure.

CONCLUSION

The prognosis for the patient with ruptured intracranial aneurysm is much more hopeful than it was just a decade ago. Advances in surgical technique and radiologic diagnosis and introduction of antifibrinolytic therapy have contributed to improved rates and quality of survival. The most important task ahead is to define those events which lead to the development of arterial vasospasm; such investigations should lead to measures for the prevention of this dread complication.

REFERENCES

1. Allcock, J. M., and Canham, P. B.: Angiographic study of the growth of intracranial aneurysms. J. Neurosurg., *45*:617–621, 1976.
2. Allcock, J. M., and Drake, C. G.: Ruptured intracranial aneurysms: the role of arterial spasm. J. Neurosurg., *22*:540–551, 1965.
3. Barno, A., and Freeman, D. W.: Maternal deaths due to spontaneous subarachnoid hemorrhage. Amer. J. Obstet. Gynecol., *125*:384–392, 1976.
4. Benoit, B. G., and Wortzman, G.: Traumatic cerebral aneurysms: clinical features and natural history. J. Neurol. Neurosurg. Psychiat., *36*:127–138, 1973.
5. Bingham, W. F.: Treatment of mycotic intracranial aneurysms. J. Neurosurg., *46*:428–437, 1977.
6. Botterell, E. H., Lougheed, W. M., Scott, J. W., et al.: Hypothermia, and interruption of carotid, or carotid and vertebral circulation, in the surgical management of intracranial aneurysms. J. Neurosurg., *13*:1–42, 1956.
7. Cajander, S., and Hassler, O.: Enzymatic destruction of the elastic lamella at the mouth of cerebral berry aneurysm? An ultrastructural study with special regard to the elastic tissue. Acta Neurol. Scandinav., *53*:171–181, 1976.
8. Crompton, M. R.: The pathology of subarachnoid hemorrhage. J. Roy. Coll. Physicians (Lond.), *7*:235–237, 1973.
9. Cruickshank, J. M., Neil-Dwyer, G., and Stott, A. W.: Possible role of catecholamines, corticosteroids, and potassium in production of electrocardiographic abnormalities associated with subarachnoid hemorrhage. Brit. Heart J., *36*:697–706, 1974.
10. Damasio, H., Seabra-Gomes, R., da Silva, J. P., et al.: Multiple cerebral aneurysms and cardiac myxoma. Arch. Neurol., *32*:269–270, 1975.
11. Davis, K. R., New, P. F. J., Ojemann, R. G., et al.: Computed tomographic evaluation of hemorrhage secondary to intracranial aneurysm. Amer. J. Roentgen., *127*:143–153, 1976.
12. Drake, C. G.: Cerebral aneurysm surgery — An update. *In* Scheinberg, P., ed.: Cerebrovascular Diseases. Proceedings of the Tenth Princeton Conference. New York, Raven Press, 1976.
13. Farhart, S. M., Schneider, R. D.: Observations on the effect of systemic blood pressure on intracranial circulation in patients with cerebrovascular insufficiency. J. Neurosurg., *27*:441–445, 1967.
14. Fisher, C. M., Roberson, G. H., and Ojemann, R. G.: Cerebral vasospasm with ruptured saccular aneurysm — the clinical manifestations. Neurosurg., *1*:245–248, 1977.
15. Flamm, E. S.: Parasurgical treatment of aneurysms. Clin. Neurosurg., *24*:240–247, 1977.
16. Flamm, E. S., and Ransohoff, J.: Treatment of cerebral vasospasm by control of cyclic adenosine monophosphate. Surg. Neurol., *6*:223–226, 1976.
17. Fodstad, H., Liliequist, B., Schannong, M., et al.: Tranexamic acid in the preoperative management of ruptured intracranial aneurysms. Surg. Neurol., *10*:9–15, 1978.
18. Grode, M. L., Saunders, M., and Carton, C. A.: Subarachnoid hemorrhage secondary to ruptured aneurysms in infants. J. Neurosurg., *49*:898–902, 1978.
19. Grubb, R. L., Raichle, M. E., Eichling, J. O., et al.: Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans. J. Neurosurg., *46*:446–453, 1977.
20. Hammer, W. J., Luessenhop, A. J., Weintraub, A. M.: Observations on the electrocardiographic changes associated with subarachnoid hemorrhage with special reference to their genesis. Amer. J. Med., *59*:427–433, 1975.
21. Hashimoto, I.: Familial intracranial aneurysms and cerebral vascular anomalies. J. Neurosurg., *46*:419–427, 1977.
22. Hayashi, M., Marukawa, S., Fujii, H., et al.: Intracranial hypertension in patients with ruptured intracranial aneurysm. J. Neurosurg., *46*:584–590, 1977.
23. Hollin, S. A., and Decker, R. E.: Effectiveness of microsurgery for intracranial aneurysms. Postoperative angiographic study of 50 cases. J. Neurosurg., *39*:690–693, 1973.
24. Hunt, W. E., Kosnik, E. J.: Timing and perioperative care in intracranial aneurysm surgery. Clin. Neurosurg., *21*:79–89, 1974.
25. Jain, K. K.: Familial intracranial aneurysms: review of literature and presentation of six new cases. Acta Neurochir., *30*:129–137, 1974.
26. Jane, J. A., Winn, H. R., Richardson, A. E.: The natural history of intracranial aneurysms: rebleeding rates during the acute and long-term period and implication for surgical management. Clin. Neurosurg., *24*:176–184, 1977.
27. Jenkins, J. S., Buckell, M., Carter, A. B., et al.: Hypothalamic-pituitary-adrenal function after subarachnoid hemorrhage. Brit. Med. J., *20*:707–709, 1969.

28. Kelly, P. J., Gorten, R. O., Grossman, R. G., et al.: Cerebral perfusion, vascular spasm, and outcome in patients with ruptured intracranial aneurysms. J. Neurosurg., 47:44–49, 1977.
29. King, R. B., and Saba, M. I.: Forewarnings of major subarachnoid hemorrhage due to congenital berry aneurysm. N.Y. State J. Med., 74:638–639, 1974.
30. Kosnik, E. J., and Hunt, W. E.: Postoperative hypertension in the management of patients with intracranial arterial aneurysms. J. Neurosurg., 45:148–154, 1976.
31. Krayenbühl, H. A., Yasargil, M. G., Flamm, E. S., et al.: Microsurgical treatment of intracranial saccular aneurysms. J. Neurosurg., 37:678–686, 1972.
32. Kurtzke, J. F.: An introduction to the epidemiology of cerebrovascular disease. *In* Scheinberg, P.: Cerebrovascular Diseases. Proceedings of the Tenth Princeton Conference. Raven Press, New York, 1976, pp. 242–247.
33. Lavyne, M. H., Kleefield, J., Davis, K. R., et al.: Giant intracranial aneurysms of the anterior circulation: clinical characteristics and diagnosis by computed tomography. Neurosurgery, 3:356–363, 1978.
34. Maurice-Williams, R. S.: Prolonged antifibrinolysis: an effective non-surgical treatment for ruptured intracranial aneurysms? Brit. Med. J., *1*:945–947, 1978.
35. Mullen, S., Hanlon, K., and Brown, F.: Management of 136 consecutive supratentorial berry aneurysms. J. Neurosurg., 49:794–804, 1978.
36. Nibbelink, D. W., Sahs, A. L., and Knowler, L. A.: Antihypertensive and antifibrinolytic medications in subarachnoid hemorrhage and their relation to cerebral vasospasm. *In* Smith, R. R., and Robertson, J. J., eds.: Subarachnoid Hemorrhage and Cerebrovascular Spasm. Springfield, Charles C Thomas, 1975, pp. 177–205.
37. Nibbelink, D. W., Torner, J. C., and Henderson, W. G.: Intracranial aneurysms and subarachnoid hemorrhage. A cooperative study. Anti-fibrinolytic therapy in recent onset subarachnoid hemorrhage. Stroke, 6:622–629, 1975.
38. Nibbelink, D. W., Torner, J. C., and Henderson, W. G.: Intracranial aneurysms and subarachnoid hemorrhage — report on a randomized treatment study. IV-A. Regulated bed rest. Stroke, 8:200–218, 1977.
39. Nornes, H.: The role of intracranial pressure in the arrest of hemorrhage in patients with ruptured intracranial aneurysm. J. Neurosurg., 39:226–234, 1973.
40. Osterman, O.: Hypothalamo-pituitary-adrenal function following subarachnoid hemorrhage. Acta Neurol. Scandinav., 52:56–62, 1975.
41. Pakarinen, S.: Incidence, aetiology, and prognosis of primary subarachnoid hemorrhage. Acta Neurol. Scand., *43* (Suppl. 29):1–127, 1967.
42. Patel, A. N., and Richardson, A. E.: Ruptured intracranial aneurysms in the first two decades of life: A study of 58 patients. J. Neurosurg., 35:571–576, 1971.
43. Peerless, S. J., and Kendall, M. J.: Experimental cerebral vasospasm. *In* Whisnant, J. P., and Sandok, B. A.: Cerebral Vascular Diseases. Proceedings of the Ninth Princeton Conference. New York, Grune and Stratton, 1974, pp. 49–58.
44. Post, K. D., Flamm, E. S., Goodgold, A., et al.: Ruptured intracranial aneurysms. Case morbidity and mortality. J. Neurosurg., 46:290–295, 1977.
45. Rosa, M.: Value of angio-tomography in planning operative treatment of internal carotid artery aneurysms. Neuroradiology, 3:82–91, 1971.
46. Saito, I., Basugi, N., and Sano, K.: Surgical treatment of intracranial aneurysms in the acute stage, with special reference to pre- and postoperative vasospasm. Excerpta Med. Int. Congr. Ser., 293:160, 1973.
47. Sakai, O., Sakata, K., Yamada, H., et al.: Familial occurrence of intracranial aneurysms. Surg. Neurol., 2:25–29, 1974.
48. Scotti, G., Ethier, R., Melancon, D., et al.: Computed tomography in the evaluation of intracranial aneurysms and subarachnoid hemorrhage. Radiology, *123*:85–90, 1977.
49. Sengupta, R. P., So, S. C., Villarejo-Ortega, F. J.: Use of epsilon aminocaproic acid (EACA) in the preoperative management of ruptured intracranial aneurysms. J. Neurosurg., *44*:479–484, 1976.
50. Shucart, W. A., and Wolpert, S. M.: Intracranial arterial aneurysms in childhood. Amer. J. Dis. Child, *127*:288–293, 1974.
51. Simeone, F. A., and Vinall, P. E.: Current concepts in the management of cerebral vasospasm. *In* Nelson, E., and Price, T. R., eds.: Cerebral Vascular Diseases. Proceedings of the Eleventh Princeton Conference. New York, Raven Press, 1978.
52. Skultety, F. M., and Nishioka, H.: Report on the Cooperative Study of Intracranial Aneurysms and Subarachnoid Hemorrhage. Section VIII. Part 2. The results of intracranial surgery in the treatment of aneurysms. J. Neurosurg., 25:683–704, 1966.
53. Slosberg, P. S.: Treatment of ruptured intracranial aneurysms by induced hypotension. Mt. Sinai J. Med., *40*:82–90, 1973.
54. Slosberg, P. S.: Nonoperative management of ruptured intracranial aneurysms. Clin. Neurosurg., *21*:90–99, 1974.
55. Soni, S. R.: Aneurysms of the posterior communicating artery and oculomotor paresis. J. Neurol. Neurosurg. Psychiat., 37:475–484, 1974.

56. Sonntag, V. K. H., and Stein, B. M.: Arteriopathic complications during treatment of subarachnoid hemorrhage with epsilon-aminocaproic acid. J. Neurosurg., *40*:480–485, 1974.
57. Stehbens, W. E.: Ultrastructure of aneurysms. Arch. Neurol., 32:798–807, 1975.
58. Sundt, T. M.: The cerebral autonomic nervous system. Mayo Clinic Proc., *48*:127–137, 1973.
59. Sundt, T. M., Jr., Onofrio, B. M., and Merideth, J.: Treatment of cerebral vasospasm from subarachnoid hemorrhage with isoproterenol and lidocaine hydrochloride. J. Neurosurg., *38*:557–560, 1973.
60. Sundt, T. M., Jr., and Whisnant, J. P.: Subarachnoid hemorrhage from intracranial aneurysms. Surgical management and natural history of disease. New Eng. J. Med., *299*:116–122, 1978.
61. Suzuki, J., Ohara, H.: Clinicopathological study of cerebral aneurysms. Origin, rupture, repair, and growth. J. Neurosurg., *48*:505–514, 1978.
62. Suzuki, J., Yoshimoto, T., and Onuma, T.: Early operations for ruptured intracranial aneurysms — study of 31 cases operated on within four days after ruptured aneurysm. Neurol. Med. Chir. (Tokyo), *18*:82–89, 1978.
63. Symon, L.: Vasospasm in Aneurysm. *In* Toole, J. F., et al., eds.: Cerebral Vascular Diseases. Proceedings of the Seventh Princeton Conference. New York, Grune and Stratton, 1970, pp. 232–240.
64. Tovi, D.: The use of antifibrinolytic drugs to prevent early recurrent aneurysmal subarachnoid hemorrhage. Acta Neurol. Scandinav., *49*:163–175, 1973.
65. VanderArk, G. D., and Pomerantz, M.: Reversal of ischemic neurological signs by increasing the cardiac output. Surg. Neurol., *1*:257–258, 1973.
66. Weintraub, B. M., McHenry, L. C., Jr.: Cardiac abnormalities in subarachnoid hemorrhage: a resume. Stroke, 5:384–392, 1974.
67. Wilkins, R. H.: Hypothalamic dysfunction and intracranial arterial spasm. Surg. Neurol., *4*:472–480, 1975.
68. Wilkins, R. H.: The role of intracranial arterial spasm in the timing of operations for aneurysm. Clin. Neurosurg., 24:185–207, 1977.
69. Winn, H. R., Richardson, A. E., and Jane, J. A.: The long-term prognosis in untreated cerebral aneurysms: I. The incidence of late hemorrhage in cerebral aneurysm: a 10-year evaluation of 364 patients. Ann. Neurol., *1*:358–370, 1977.
70. Yasargil, M. G., and Fox, J. L.: The microsurgical approach to intracranial aneurysms. Surg. Neurol., 3:7–14, 1975.
71. Yoshimoto, T., Uchida, K., Kaneko, U., et al.: An analysis of follow-up results of 1000 intracranial saccular aneurysms with definitive surgical treatment. J. Neurosurg., *50*:152–157, 1979.
72. Zervas, N. T., Candia, M., Candia, G., et al.: Reduced incidence of cerebral ischemia following rupture of intracranial aneurysm. Surg. Neurol. (in press).

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The Pathogenesis and Medical Treatment of Extrapyramidal Disease

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Since the direct motor pathways from cerebral cortex to muscle have been analyzed with considerable precision, the physiological basis of motor function is well understood in relation to pyramidal and neuromuscular disease. The roles of the basal ganglia and the cerebellum remain elusive, but current views emphasize the importance of the former in putting together the neurophysiological plan required for executing the movement, and stress the part played by the latter in evaluating information fed back on the progress of the movement. Expressing these ideas in the terminology of the computer era, the basal ganglia appear to be concerned primarily with the assembly of a program for movement, while the cerebellum is monitoring and continuously correcting errors that develop during implementation of the program.

There is a wide conceptual gap between this theoretical framework of motor function and the clinical features of neurological diseases involving the motor pathways. The salient feature of extrapyramidal disorders is the presence of involuntary movements. The pathological basis includes lesions of the basal ganglia (caudate, putamen, pallidum, subthalamic nucleus) and the brain stem (substantia nigra, red nucleus, locus ceruleus). Some workers classify lesions of the cerebellar pathways as extrapyramidal, and certainly the deficits associated with cerebellar disorders can encompass certain involuntary movements. However, since cerebellar syndromes comprise a relatively clearly defined clinical and pathological picture, it is convenient to separate them from other disorders of movement. In summary, therefore, diseases of the motor system may be classified as follows:

1. Extrapyramidal: dominated by the presence of involuntary movements.

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2. Pyramidal: weakness associated with increased tendon reflexes and abnormal superficial reflexes.

3. Cerebellar: ataxia in spite of normal proprioception, often accompanied by nystagmus.

4. Neuromuscular: weakness often associated with muscle wasting, reduced tendon reflexes, or fatigability.

While there may be important additional features, such as changes in tone or posture, the above criteria are the simplest definitive findings upon which separation of the major syndromes of movement disorders can be based.

The subclassification of extrapyramidal syndromes is difficult and unsatisfactory. The most practical approach is clinical, dividing the various categories of extrapyramidal disorder according to their motor manifestations. While logical, this seemingly straightforward classification encounters major problems because many involuntary movements are not easily placed into one or other of the major types that are clinically recognized, and different kinds of movement often occur in the same patient. Nevertheless, until new information becomes available to improve the basis of classification, clinical features remain the least unsatisfactory criteria for separating extrapyramidal disorders. In this review, we shall consider, in turn, tic, chorea, athetosis, dystonia, ballism, and parkinsonism.

TIC

Tics are rapid, stereotyped movements which are erratic, spasmodic and purposeless; involuntary noises or words are included. The classification of tics is based upon age of onset, course, and distribution. Separate categories identified by Sweet et al.[19] include transient tic of childhood, chronic simple tic, persistent simple and multiple tic of childhood or adolescence, and chronic multiple tic (Gilles de la Tourette syndrome).

There is no established neuropathological basis for tic, although an unconfirmed report on one patient with Tourette's syndrome has suggested a maturational arrest of small cells in the caudate nucleus.[4]

The most effective treatment of tic is haloperidol, but since this drug induces prominent adverse reactions, therapy should be undertaken only in patients who are substantially disabled by their symptoms, notably those with severe Tourette's syndrome. The majority of such patients derive some benefit from haloperidol. The usual unwanted reactions to haloperidol are akinesia, akathisia, dyskinesia, and constipation.

The use of haloperidol in the management of tic is empirical, but this drug is known to be a potent antagonist of dopaminergic receptors. It can therefore be inferred that the pathophysiology of tic probably involves a disturbance in the balance of central neurotransmitters or neuromodulators that results in a relative excess of dopaminergic function.

CHOREA

Choreatic movements are fast, predominantly distal and sufficiently complex for the term semipurposive to have been coined to describe them. While the neurophysiology of these movements is not understood there are important clues to their biochemical and morphological pathogenesis. Biochemically, the critical observations are (1) drugs which increase dopaminergic transmission in the brain, such as levodopa, induce chorea, whereas (2) agents which decrease dopaminergic function, such as chlorpromazine, alleviate chorea. These findings indicate that choreatic movements are related to a relative predominance of dopaminergic transmission in certain regions of the brain. Conventional morphology provides evidence on the area of the brain that is involved. In the commonest form of chronic chorea, Huntington's disease, the major pathological change is loss of neurons in the caudate nucleus and putamen. It can therefore be concluded that chorea is likely to derive from a relative excess of dopaminergic function in the striatum. The possibility remains that other transmitters (such as gamma aminobutyric acid) and other parts of the brain (such as the globus pallidus) may also be involved, but the supporting evidence is less complete.

Huntington's Disease

This dominantly inherited disorder has been investigated extensively over the last decade. Particular interest has been focused on the depletion, in this disease, of gamma aminobutyric acid (GABA) and glutamic acid decarboxylase — the enzyme responsible for converting glutamic acid to GABA.[2, 16] Attempts have been made to augment levels of GABA by administering glutamate, but they have not achieved any therapeutic response. Similarly, efforts have been made to impede the degradation of GABA with valproate, a drug which is thought to inhibit GABA transaminase and succinic semialdehyde dehydrogenase. However, maximum tolerated doses of valproate have not been found to alleviate Huntington's disease. Another approach to enhancing GABA function has been treatment with muscimol, an artificial agonist of GABA which acts directly upon GABAergic synaptic receptors. Unfortunately, this endeavor has also failed to elicit any consistent worthwhile result.

The only drugs to have been demonstrated to alleviate chorea are agents which antagonize dopamine by depletion (e.g., tetrabenazine) or receptor blockade (e.g., haloperidol). Such agents have prominent unwanted actions, so they must be used cautiously. Tetrabenazine can cause severe depression, and since Huntingtonian patients are commonly depressed before therapy, the use of a drug which may exacerbate this problem should be weighed carefully. The main drawback with butyrophenones (such as haloperidol) and phenothiazines (such as perphenazine) is the risk of inducing tardive dyskinesia.

In spite of their limitations, any of these antidopaminergic drugs may be cautiously employed to treat Huntingtonian patients who are badly disabled by their involuntary movements.[6, 18]

Other Forms of Chorea

Chorea may be produced by certain generalized diseases, such as thyrotoxicosis, hepatolenticular degeneration, and systemic lupus erythematosus; the correct treatment is that of the underlying disorder. Chorea can be induced by various drugs, such as oral contraceptives, phenytoin, anticholinergics, amphetamine, methylphenidate, levodopa, and neuroleptics (acute dyskinesia and tardive dyskinesia). In all of these, the causal drug should be withdrawn if possible. Sydenham's chorea is reported to respond to dopamine blocking agents, but usually the involuntary movements are sufficiently mild and transitory to be managed without the use of drugs. In benign hereditary chorea and senile chorea, therapeutic considerations are similar to those outlined in the discussion of Huntington's disease.

ATHETOSIS

Athetoid movements are slow, coarse, and writhing. They may be quite varied, and often include choreic components, this combination being designated choreoathetosis.

Causes of athetosis include infection, vascular disease, cerebral palsy, kernictrus, and idiopathic degeneration associated with hypermyelination (état marbré or status marmoratus). The morphological lesion involves the basal ganglia, but its biochemical features are not known. There is neither rational nor empirical treatment for this disorder.

Choreoathetosis may be regarded as a variant of chorea. The diagnosis and management of patients with this form of involuntary movement is pursued in the same way as chorea.

DYSTONIA

Dystonic movements are relatively slow and sustained, characteristically leading to abnormal postures; they may occur in isolation or in association with almost any other extrapyramidal disorder. The movement may be focal or generalized; the commonest example of the former is torticollis, and the most frequent manifestation of the latter is hereditary torsion dystonia (dystonia musculorum deformans).

Dystonia is one of the least understood of all disorders of movement. Neither the biochemical nor the morphological pathology is known, although there have been reports that dopamine metabolites are diminished in the ventricular fluid of patients with autosomal dominant torsion dystonia.[20] It has also been claimed that in this disease the plasma concentration of dopamine beta hydroxylase is elevated.[12] Dopamine beta hydroxylase is the enzyme responsible for converting dopamine to norepinephrine, but the significance of the alleged enzymic abnormality is obscure. The treatment of both focal and generalized dystonia is as unsatisfactory and frustrating as our under-

standing of its cause. There are no adequately controlled studies demonstrating that any therapy has any consistent effect on any form of dystonia. However, Fahn has recently reported promising results with very high doses of anticholinergic agents in children with torsion dystonia.[7a]

BALLISM

Ballismic movements predominantly involve proximal limb muscles; most frequently there are violent rotational or flinging displacements of an arm (hemiballism). The cause is usually a vascular lesion affecting the subthalamic nucleus, but infarcts of other structures, such as the dorsomedial nucleus of the thalamus, can also be responsible. While there is no direct evidence concerning the biochemical pathology, it has been found that hemiballism often responds well to dopaminergic blocking drugs such as perphenazine or haloperidol.[11, 13] It is therefore probable that a relative excess of dopaminergic activity plays a part in releasing this syndrome. In some patients the drugs employed to alleviate hemiballism can be withdrawn after a few months, without recurrence of the involuntary movements.

PARKINSONISM

Parkinsonism is the most common of the disorders of the extrapyramidal nervous system. Indeed it ranks as one of the most prevalent of the primary disorders of the central nervous system.

Diagnosis

Parkinsonism is a clinical syndrome with three cardinal features: tremor at rest, rigidity, and hypokinesia. When all three signs are present there is no difficulty in making the diagnosis. Usually only one sign is seen at first and at this time diagnosis may present a challenge.

In advanced disease other features of parkinsonism may be seen: hypomimia, stooped posture, primitive reflexes, difficulty with eye movements (particularly convergence), decreased blinking, blepharoclonus, dysphonia, dysarthria, palilalia, drooling, diminution of associated movements, micrographia, festination, propulsion, retropulsion, akathisia, ulnar deviation of fingers, foot inversion, oiliness of the skin, depression, and eventually impaired cognitive function.

Typically, the patient is a male (60 per cent) aged about 50 to 60 years, who presents with an insidiously progressive resting tremor (70 per cent) at a frequency of 4 to 6 Hz, amplified by anxiety. The differential diagnosis of resting tremor is wide and includes that due to essential tremor, familial tremor, senile tremor, Wilson's disease, thyrotoxicosis, mercury poisoning, and neurosyphilis. An action or in-

tention tremor may be associated with the resting tremor of parkinsonism.

With progression of the disease, rigidity and hypokinesia usually develop and nearly always begin at the site of initial tremor. Parkinsonian rigidity is sometimes difficult to separate from the pyramidal sign of spasticity.

It is advisable to examine the spinal fluid because the presence of oligoclonal bands suggests the possibility of postinfectious parkinsonism.[21] Delay in the confirmation of the diagnosis of primary parkinsonism is probably not detrimental. Although there is not general agreement, most neurologists would now advocate withholding the most effective treatment, levodopa, until it is really necessary, since an appreciable number of patients only benefit from this therapy for a limited period.[8] The stage at which levodopa should be started must be decided on an individual basis, depending upon such factors as whether their illness is jeopardizing the patient's income, domestic life, or psychological status.

Classification

Although the diagnosis of parkinsonism is easy in typical cases, an attempt should be made to differentiate the subclasses of this syndrome in order to determine management and prognosis. Parkinsonism is most appropriately subdivided into three major groups—primary or idiopathic, secondary or symptomatic, and the paraparkinsonian syndromes (also termed "parkinson's plus" by Fahn[7]).

The most common form of parkinsonism is the primary or idiopathic type, which has a relative prevalence of 7 out of every 8 cases of parkinsonism. In a minority of these cases a family history of parkinsonism can be established: when this is present the pattern of inheritance is usually autosomal dominant with incomplete penetrance.

The next most common form of parkinsonism is secondary or symptomatic parkinsonism. Fifty years ago the postinfectious (particularly von Economo encephalitis) group was prevalent, but drug reactions are now the most frequent cause of secondary parkinsonism. Etiologic agents include phenothiazines, butyrophenones, reserpine, and tetrabenazine.

The third group of syndromes are the paraparkinsonian disorders. Here parkinsonism is only a part of the total picture and yet early diagnosis may make a significant difference in long-term outcome particularly in Wilson's disease and normal pressure hydrocephalus. From a prognostic point of view, separating this group from primary parkinsonism is particularly important. Included in the paraparkinsonism syndromes are Shy-Drager syndrome, Steele-Richardson-Olszewski syndrome, Wilson's disease, Hallervorden-Spatz disease, Huntington's disease (rigid form), striatonigral degeneration, olivopontocerebellar degeneration, pallidal atrophy (juvenile parkinsonism), Jakob-Creutzfeldt disease, normal pressure hydrocephalus, parkinsonian dementia complex of Guam, hypoparathyroidism, idiopathic calcification of the basal ganglia, and toxic reactions to carbon monoxide, carbon disulfide, and manganese.

Pathology

The most consistent pathologic changes in parkinsonism are found in the substantia nigra. Even with the naked eye, depigmentation permits the assumption of parkinsonism by the pathologist. Accompanying the loss of pigment there is a loss of neurons, which is greatest in the zona compacta of the substantia nigra where there is a reactive gliosis and occasional phagocytosis. Other pigmented areas of the brain which show a similar cell loss include the locus ceruleus and dorsal motor nucleus of the vagus. The vast majority of idiopathic parkinsonian brains have Lewy bodies in the cytoplasm of neurons, particularly within the substantia nigra and locus ceruleus. The severity of parkinsonism seems to correlate with the degree of neuronal loss in the substantia nigra, but as the severity of the syndrome increases more diffuse pathology is found.

Postinfectious (postencephalitic) parkinsonism has fewer Lewy bodies and more neurofibrillary tangles, with a greater degree of gliosis and cell loss in the substantia nigra than in the locus ceruleus. However, in this form of parkinsonism, the upper brain stem is predominantly affected, while idiopathic parkinsonism is a systemic disorder primarily affecting pigmented neurons.

Regardless of etiology, parkinsonism can be considered to be a neostriatal dopamine deficiency syndrome. In one case report of predominantly unilateral parkinsonism, the neostriatum contralateral to neurological deficits showed a 50 per cent loss in dopamine concentration compared to the near normal ipsilateral neostriatum. There was no asymmetry in the brain serotonin and norepinephrine levels. By the time the clinical features of parkinsonism become apparent, the brain concentration of dopamine has already undergone substantial reduction, implying that compensatory mechanisms are available to mask the preclinical but biochemically evident early stage of the disease.

Apart from the characteristic loss in brain dopamine and its metabolites in parkinsonism, there is a variable decrease in norepinephrine, L-aromatic aminoacid decarboxylase, glutamic acid decarboxylase, serotonin, and its metabolites.

Pathophysiology

One of the major areas of ignorance in the current concept of parkinsonism is the causal chain of events by which striatal dopamine depletion leads to tremor, rigidity and akinesia. At the risk of oversimplification, the following hypotheses are at present the subject of investigations designed to elucidate by confirmation or refutation.

(1) Tremor appears to result from instability of a central feed-back circuit which is accessible to modulation by peripheral input.

(2) Rigidity is causally related to increased resting muscle activity, which correlates with augmented long latency reflex responses to stretch.

(3) Akinesia seems to arise in some way from a failure of the mechanism responsible for assembling the encoded program of neurophysiological activity that constitutes the planning of a movement—

the putting together of a complex pattern of spatially and temporally linked neuronal excitation and inhibition, that is, the blue-print for the movement.

Etiology

The cause of primary parkinsonism remains obscure. Current hypotheses include infection with an unconventional virus, an abnormal reaction to a common virus, exposure to an unidentified toxic agent, or some form of premature or accelerated aging. These are not mutually exclusive alternatives. One of the most plausible although somewhat loosely formulated views invokes selective vulnerability of the nigrostriatal pathway; increasing age is regarded as predisposing the nigrostriatal system to damage by some relatively ubiquitous environmental hazard. It may be that cumulative exposure to an etiological factor eventually leads to neuronal death, or that normal protective mechanisms become less effective with advancing age. It is notable that in parkinsonism there is an exaggeration of a number of trends that can be recognized as the years pass in normal subjects. These include, at the biochemical level; a reduction of dopamine and its metabolites in the brain, a decrease in the enzyme tyrosine hydroxylase (which is responsible for the rate limiting step in dopamine synthesis) and a fall in tetrahydrobiopterin (the cofactor for tyrosine hydroxylase). Morphologically, parkinsonism is characterized by a more severe depletion of substantia nigra neurons than that normally encountered in the elderly. The physiological disturbances that underlie the rigidity of parkinsonism — high resting electromyographic levels and enhanced long latency responses to stretch — are also seen in old subjects without parkinsonism (albeit to a lesser extent). Finally, some of the clinical features of parkinsonism, such as the flexed posture and shuffling gait, are almost a caricature of the normal clinical picture of senescence.

Treatment

Despite advances in treatment over the last 20 years, primary parkinsonism continues to be a progressive disorder. Levodopa and dopamine agonist drugs are the most powerful therapeutic agents available, but they lead to troublesome clinical fluctuations and behavioral changes after long-term treatment. In an effort to prolong useful independent life in parkinsonian patients, it is probably wise to start with the minimal necessary supportive therapy (including drugs), sufficient to maintain function even if at the price of continued evidence of parkinsonism.

Primary parkinsonism may remain static for years or only progress minimally. An emotionally stable parkinsonian can often function well socially and economically without drugs, the use of which should be postponed until activities of daily living are disturbed. Amantadine, anticholinergics or combinations of these agents can be tried when pharmacotherapy becomes necessary; eventually levodopa will be required. The effectiveness of levodopa will not be lost by waiting, so it should be used when it is needed most.

The literature on the surgical treatment of parkinsonism is extensive, but current indications for surgery are few. The symptoms most commonly relieved by destruction of the ventrolateral nucleus of the thalamus are tremor and rigidity of the opposite limbs. Unfortunately the general signs which are not lateralized, such as defects of gait, posture and speech, are minimally benefitted by surgery. Hoehn and Yahr[10] reported the follow-up on 150 patients seen before and after stereotactic surgery for parkinsonism — only 4.7 per cent of the patients showed sustained increase in functional ability. Bilateral surgery led to complications which were twice as common as seen with unilateral procedures and were also more severe.

Levodopa is still the most effective drug for the control of parkinsonism and the incorporation of an inhibitor of extracerebral aromatic aminoacid decarboxylase (as in Sinemet and Madopar) avoids some of the peripheral side effects seen with levodopa alone.

Recent studies suggest that there exist more than one type of dopamine receptor. This hypothesis has important implications for parkinsonism because if true, it should be possible to develop drugs which selectively activate or block one category of receptors without affecting another. In this way, centrally induced adverse reactions might be reduced without compromising efficacy. At this time, however, levodopa remains the most satisfactory drug for the treatment of primary parkinsonism.

Specific Drug Therapy. The most useful pharmacological paradigm of parkinsonism is neurotransmitter imbalance — too little dopamine or too much acetylcholine. To correct this pathopharmacologic state it is desirable either to increase dopaminergic effects or to reduce cholinergic function, or both. The pharmacotherapy of parkinsonism therefore comprises drugs acting primarily on the dopaminergic system, and agents acting primarily on the cholinergic system.

Drugs Acting Primarily on the Dopaminergic System. Levodopa derives its pharmacological activity from formation of its active metabolite, dopamine. The enzyme responsible for this transformation is the relatively ubiquitous L-aromatic aminoacid decarboxylase. The therapeutic index of levodopa has been increased by concomitant administration of decarboxylase inhibitors which do not readily cross the blood-brain barrier. This pharmacokinetic manipulation results in a reduction of adverse reactions produced by dopamine formed outside the blood-brain barrier. Decarboxylase inhibitors such as carbidopa (in Sinemet) or benserazide (in Madopar) decrease emesis, hypotension, and the risk of inducing cardiac arrhythmias or glaucoma. They also lead to a 75 per cent reduction in the dose of levodopa required. Unfortunately unwanted effects generated inside the blood-brain barrier, such as dyskinesia and psychosis, persist as major limitations of levodopa therapy.

Other attempts to improve levodopa therapy by enzymic inhibition include: (1) selective blockade of monoamine oxidase B (involved in intracellular degradation of dopamine) with deprenyl. This appears to extend the half-life of levodopa and decrease "wearing-off" reactions and end-of-dose akinesia.[15] (2) Selective blockade of calechol-O-

methyltransferase (involved in extracellular degradation of dopamine) with U-0521. Encouraging observations in animals[9] will no doubt lead to clinical evaluation.

Several drugs have been developed in an attempt to stimulate dopamine receptors selectively. Most have been found to be inferior to levodopa and some have serious side-effects e.g., apomorphine, N-propyl-noraporphine, lergotrile. The only clinically useful dopamine agonist currently available is bromocriptine.[3]

The converse approach to selective agonism (designed to elicit wanted dopaminergic effects without inducing undesirable reactions) is selective antagonism (designed to block unwanted dopaminergic effects without inhibiting desirable responses). In the quest for dopaminergic antagonists which might ameliorate dyskinesia or psychosis, two drugs appear promising — oxiperomide[1] and tiapride.[17] Further clinical investigation will be necessary before their therapeutic potential can be evaluated.

DRUGS ACTING PRIMARILY ON THE CHOLINERGIC SYSTEM. Anticholinergic drugs such as trihexyphenidyl and benztropine ameliorate parkinsonism by blocking muscarinic receptors. Adverse effects include blurred near vision, dryness of the mouth, constipation, disturbances of micturition, impairment of memory, confusion, delusions, hallucinations and somnolence.

Antihistamines have some mild anticholinergic properties and may be of help in parkinsonism; the main adverse effect of these drugs is sedation.

Tricyclic antidepressants may be useful in the treatment of parkinsonism. They can reduce motor deficits because of their anticholinergic action; their antidepressant properties may also be beneficial. Side effects include sedation and hypotension.

Amantadine can help in mild to moderate parkinsonism. Its mode of action is not known, but it does possess anticholinergic properties. The action of amantadine often declines after 3 to 6 months of treatment. Toxic effects are livedo reticularis, edema, confusion, delusions, dry mouth, and blurred vision.

Therapeutic Problems

INADEQUATE THERAPEUTIC RESPONSE. Early. When patients fail to improve following the initial administration of normal doses of levodopa, a diagnosis other than primary parkinsonism should be suspected. In particular, the possibility of Shy-Drager syndrome, Steele-Richardson-Olszewski syndrome, or striatonigral degeneration should be considered.

Late. Sometimes efficacy declines after several years of satisfactory therapeutic response to levodopa. The mechanism underlying this problem is not understood. There may be simple progression of the neuropathology of Parkinson's disease, but there is also evidence to indicate that chronic administration of levodopa may decrease the concentration of dopamine receptors in the brain.[14]

FLUCTUATIONS IN THERAPEUTIC RESPONSE. "Wearing-off" reac-

tions. These fluctuations are a consequence of the pharmacokinetics of levodopa. The plasma half-life of the drug is less than 3 hours, so patients often notice a rather abrupt deterioration in their parkinsonism at the end of the interval between doses. This problem can sometimes be alleviated by more frequent administration of smaller doses.

"On-off" reactions. These abrupt fluctuations characteristically occur without any temporal relationship to the last dose of levodopa and attempts to correlate clinical changes with alterations in the plasma concentration of levodopa give conflicting results. Temporary but substantial (80 per cent) reduction in the dose of levodopa may be helpful,[5] and in some patients improvement has been achieved by a combination of bromocriptine with some 50 per cent of the previous dose of levodopa.[3] Unfortunately, however, "on-off" reactions often remain refractory to all attempts at therapeutic intervention.

Adverse Reactions. The commonest serious adverse reactions to levodopa are dyskinesia and psychiatric disturbances.

Dyskinesia. Dyskinesia is the most frequent dose-limiting side-effect of levodopa. In occasional patients, it occurs at such a low initial level of drug intake that no therapeutic response can be elicited. In other patients, who have done well on normal doses of levodopa for a number of years, dyskinesia becomes more severe despite the same dose of levodopa throughout the period of treatment. In both situations, improvement can sometimes be achieved by reducing levodopa and adding bromocriptine.

Psychiatric Reactions. Severe parkinsonsim can, by itself, lead to depression and dementia. In addition, all the drugs employed to treat parkinsonism may exacerbate confusion, impair memory, and induce hallucinations and delusions. Psychiatric symptoms may be particularly troublesome with bromocriptine, but levodopa is also responsible in many cases. These reactions can present one of the most frustrating dilemmas that occur in the management of parkinsonism. The dose of the causal drug must be reduced to improve the patient's mental state, but this inevitably leads to an increase in neurological deficits. Occasionally, no acceptable compromise can be found: in order to protect the patient from the potentially lethal complications of aspiration, a dose of levodopa must be given which is still sufficient to sustain a florid psychotic reaction. Attempts to reduce the levodopa in this setting will jeopardize the life of the patient.

CONCLUSION

It is evident that our understanding of the extrapyramidal syndromes is extremely patchy. Dystonia and athetosis are disorders which share unsatisfactory nosology, unknown pathology, and unrewarding therapy. Tic, ballism, and chorea are also poorly understood, but they can be alleviated by empirical treatment with dopamine antagonists, although these drugs induce prominent adverse reactions. For parkinsonism, by far the commonest extrapyramidal disease, there

have been spectacular successes in elucidating the morphological, biochemical, physiological, and pharmacological abnormalities. Nevertheless, there remain major areas of ignorance such as the cause of idiopathic parkinsonism, and the role of neurotransmitters and neuromodulators other than dopamine. Enthusiastic reporting of the substantial improvement achieved with dopaminergic drugs has been followed by dismay at the refractoriness of the late problems with levodopa therapy. The extrapyramidal diseases are likely to continue to be a fertile if at times frustrating field for future research.

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REFERENCES

1. Bédard, P., Parkes, I. D., and Marsden, C. D.: Effect of new dopamine-blocking agent (oxiperomide) on drug-induced dyskinesias in Parkinson's disease and spontaneous dyskinesias. Brit. Med. J., *1*:954–956, 1978.
2. Bird, E. D., and Iversen, L. L.: Huntington's chorea: post-mortem measurement of glutamic acid decarboxylase, choline acetyltransferase and dopamine in basal ganglia. Brain, *97*:457–472, 1974.
3. Calne, D. B., Williams, A. C., Neophytides, A., et al.: Long-term treatment of parkinsonism with bromocriptine. Lancet, *1*:735–738, 1978.
4. Clauss, J. F., and Balthazar, K.: Zur Kenntness der generalisierten Tic-Krankheit (Maladie des Tic, Gilles de la Tourette). Arch. Psychiatr. Nervenkr., *191*:398–418, 1954.
5. Direnfeld, L., Spero, L., Marotta, J., et al.: The L-dopa on-off effect in Parkinson's disease: treatment by transient drug withdrawal and dopamine receptor resensitisation. Ann. Neurol., *4*:573–575, 1978.
6. Fahn, S.: Treatment of choreic movements with perphenazine. *In* Barbeau, A., Chase, T. W., Paulson, G. W., eds.: Advances in Neurology. New York, Raven Press, 1973, Vol. 1, pp. 755–763.
7. Fahn, S.: Secondary parkinsonism. *In* Goldensohn, E. S., and Appel, S. H., eds.: Scientific Approaches to Clinical Neurology. Philadelphia, Lea and Febiger, 1977, Vol. 2, pp. 1159–1189.

7a. Fahn, S.: Treatment of dystonia with high dosages of anticholinergic medication. (Abstract.). Neurol. (Minneap.), *29*:605, 1979.

8. Fahn, S., and Calne, D. B.: Considerations in the management of parkinsonism. Neurology, *28*:5–7, 1978.
9. Fahn, S., Comi, R., and Snider, S. R.: Effect of COMT inhibitor U-0521, with levodopa administration. 4th International Catecholamine Symposium (Asilomar Conference Center, Pacific Grove, California) 17–22 Sept. 1978.
10. Hoehn, M. M., and Yahr, M. D.: Evaluation of the long term results of surgical therapy. *In* Gillingham, F. J., and Donaldson, I. M. L., eds.: Third Symposium on Parkinson's Disease, Edinburgh, E and S. Livingstone, 1969.
11. Johnson, W. G., and Fahn, S.: Treatment of vascular hemiballism and hemichorea. Neurology, *27*:634–636, 1977.
12. Kanter, W., Wooten, G. F., and Eldridge, R.: Dopamine β-hydroxylase and the torsion dystonias. *In* Eldridge, R., and Fahn, S., eds.: Advances in Neurology. New York, Raven Press, 1976, Vol. 14, pp. 303–305.
13. Klawans, H. L., Moses, H., Nausieda, P. A., et al.: Treatment and prognosis of hemiballismus. New Engl. J. Med., *295*:1348–1350, 1976.
14. Lee, T., Seeman, P., Rajput, A., et al.: Receptor basis for dopaminergic supersensitivity in Parkinson's disease. Nature, *273*:59–61, 1978.
15. Lees, A. J., Shaw, K. M., Kohout, L. J., et al.: Deprenil in Parkinson's disease. Lancet, *3*:791–794, 1977.
16. Perry, T. L., Hansen, S., and Kloster, M.: Huntington's chorea: deficiency of γ-aminobutyric acid in the brain. New Engl. J. Med., *288*:337–342, 1973.

17. Price, P., Parkes, J. D., and Marsden, C. D.: Tiapride in Parkinson's disease. Lancet, 2:1106, 1978.
18. Shoulson, I., and Chase, T. N.: Huntington's disease. Ann. Rev. Med., 26:419–426, 1975.
19. Sweet, R. D., Bruun, R. D., Shapiro, A. K., et al.: The pharmacology of Gilles de la Tourette's syndrome (chronic multiple tic). *In* Klawans, H. L., ed.: Clinical Neuropharmacology. New York, Raven Press, 1976, Vol. 1, pp. 81–105.
20. Tabaddor, K., Wolfson, L. I., and Sharpless, N. S.: Diminished ventricular fluid dopamine metabolites in adult onset dystonia. Neurology, 28:1254–1258, 1978.
21. Williams, A., Houff, S., Lees, A., et al.: Oligoclonal banding in the CSF of patients with post-encephalitic parkinsonism. J. Neurol. Neurosurg. Psychiatry (in press).

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Multiple Sclerosis

A Critical Update

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The past several years have seen an enormous proliferation of the literature of multiple sclerosis, reflecting intensive research activity in numerous areas. Much of it has recently been reviewed in great detail elsewhere[35] and can only be summarized here. Virology, immunology, epidemiology, genetics, neurophysiology, and radiology have all contributed new information. Unfortunately much of it has been contradictory and controversial. The results of some of the newer diagnostic techniques are forcing a re-examination of long held ideas regarding the natural history of the disease and its pathogenesis.

Two major hypotheses regarding etiology and pathogenesis continue to dominate research in multiple sclerosis: the search for a single, specific causative viral agent with prolonged latency, and the discovery of an altered immunologic status, based upon the animal model of experimental allergic encephalomyelitis. In spite of very large amounts of time and money spent on these endeavors, knowledge of the etiology and the exact pathogenesis of the disease still eludes us. No reliable laboratory test for the diagnosis or for the measurement of the activity of the disease has become available.

Because of these factors, therapeutic regimens, many of which reflect a rather naive understanding of the natural history and pathology of multiple sclerosis have been proposed in support of a particular hypothesis, ranging from the reasonable to the outlandish.[41]

ETIOLOGY AND PATHOGENESIS

Virology and Immunology

The search for a single, specific slow viral infection continues unabated. The reports by Carp et al.[6] and by Henle et al.[20] of an agent

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associated with multiple sclerosis have been refuted by others.[8, 25] Burks[3] claims to have recovered a corona virus from the brains of 2 patients with multiple sclerosis and Mitchell et al.[28] have reported isolating from the bone marrow of 4 patients with multiple sclerosis a filterable agent which causes a cytopathic effect in cell cultures, an effect which can be passed to further cultures. Both of these reports await confirmation. The large numbers of papers dealing with immunologic studies in multiple sclerosis are characterized by the extraordinary inconsistency of their results and have led to little useful information. There is an almost obsessive preoccupation with measles as the culprit in spite of the publications of many studies which fail to establish a reasonable association of this agent with multiple sclerosis. Fuccillo et al.[16] studied 108 patients with multiple sclerosis who had an increase in serum measles antibodies but found no evidence of altered cellular immunity to measles, cytomegalovirus, herpes virus I and II or vaccinia. Raine et al.[38] investigated active demyelinating central nervous system lesions in acute and chronic multiple sclerosis using peroxidase-conjugated antimeasles antibody but found no evidence of measles antigen. Symington and Mackay[45] studied lymphocyte reactivity to measles, parainfluenza and vaccinia virus in 12 patients with early multiple sclerosis and failed to demonstrate any difference in activity from a control group. They suggest that the deficient cellular response to measles virus and possibly to other common viruses is a consequence of the disease itself and not a causal factor.

Abnormalities of cell-mediated immunity have been reported in patients with multiple sclerosis. Several studies have suggested that patients with multiple sclerosis manifest a broad-based depression of cell-mediated immunity, while other studies do not. Evidence of increased cell-mediated immunity to neural antigens in patients with multiple sclerosis has also been observed by some groups but not by others based upon various *in vitro* correlates of cell-mediated immunity including antigen-induced lymphocyte transformation or proliferation, macrophage migration inhibition, direct leukocyte migration inhibition and inhibition of macrophage migration in electrical fields.[35] Lisak et al.[23] found hyporesponsiveness of leukocytes to myelin basic protein, central nervous system extract, crude measles antigen, purified measles nuclear core, and other viral antigens, but failed to show a difference in the pattern of reactivity in a small group of patients with active multiple sclerosis compared with normal subjects, regardless of the stage of clinical disease. They concluded that this hyporesponsiveness found to measles and other viruses in studies of large groups of patients with multiple sclerosis using the buffy coat migration techniques as well as the increased serum and cerebrospinal fluid antibodies to several of the viruses may represent a broad-based deficit in immunologic control and feedback mechanisms, and does not imply a particular viral etiology of multiple sclerosis.

Levy et al.[22] have reported that lymphocytes from patients with multiple sclerosis form rosettes around measles-infected cells, thus giving an important boost to the measles theory by claiming 100 per cent

accuracy in diagnosis. Unfortunately, they did not perform similar tests on the siblings of their patients with multiple sclerosis. Offner et al.[31] were the most recent to report that while there were significantly more rosettes formed by lymphocytes from patients with multiple sclerosis, there was considerable overlap between the two groups.

Antel et al.,[1] in a study of the mitogen responsiveness and suppressive cell function in multiple sclerosis, found reduced T-cell responsiveness to mitogens. The number of circulating T-cells was reduced, but the number of B-cells was preserved. They pointed out that these abnormalities may well reflect the genetic endowment of patients with multiple sclerosis, rather than being related to a specific viral infection. In fact, several authors[2, 14, 32] have demonstrated that the high viral titers to measles found in their patients with multiple sclerosis were associated with histocompatibility type rather than with multiple sclerosis.

That some kind of association between measles and multiple sclerosis exists is undeniable, but there is ample evidence to suggest that other viruses play a similar role.[35] That viral infection plays an important role in the pathogenesis of multiple sclerosis appears to be inescapable; that a single, specific viral agent is responsible for the disease appears highly unlikely. In the absence of an animal model of the disease, it is going to be extremely difficult to actually prove that any agent isolated from brain or other tissue in patients with multiple sclerosis is the causative agent. Immunologic studies to date have yet not established if multiple sclerosis is the result of a hyperimmune state or a cellular immunodeficiency although the latter possibility, when coupled with the fragmentary genetic data, appears to be more promising.

Relationship with Experimental Allergic Encephalomyelitis

The lack of an animal experimental model for multiple sclerosis has frustrated investigators for many years. That experimental allergic encephalomyelitis (EAE) may indeed be such a model appears to have received considerable support from the work of Wisniewsky and Keith,[49] who reported having produced a spontaneously remitting and recurrent disease in guinea pigs with histologic lesions which are quite reminiscent of multiple sclerosis. The presence of bizarre, multinucleated glial cells, however, should raise the possibility of a relationship with another demyelinizing condition, progressive multifocal leukoencephalopathy. Furthermore, recurrent episodes of the human equivalent of experimental allergic encephalomyelitis, disseminated vasculomyelinopathy, though rare, are not unknown.[37]

At the present time, in spite of much evidence to the contrary,[35] the experimental allergic encephalomyelitis model is still being pursued with enthusiasm and vigor. Whitaker[47] made an important contribution to the study of this problem when he examined the distribution of myelin basic protein in central nervous system lesions of both multiple sclerosis and experimental allergic encephalomyelitis. Marked diminution of reactivity with anti-myelin basic protein occurred in early lesions of multiple sclerosis and extended far beyond

any identifiable inflammatory elements; in both parenchymal and perivascular areas, lipid laden macrophages in plaques of multiple sclerosis frequently contained myelin basic protein. In experimental allergic encephalomyelitis, however, myelin basic protein was relatively well preserved in the brains of guinea pigs. Normal appearing patterns of myelin basic protein existed adjacent to the perivascular cellular infiltrates and macrophages containing myelin basic protein were rare. Whatever mechanism or mechanisms in multiple sclerosis promote loss of myelin basic protein, the loss is marked once the process is initiated. Reactivity of anti-myelin basic protein with normal white matter in brain tissue from patients with multiple sclerosis could not be distinguished from that of normal brain.

On the other hand, in experimental allergic encephalomyelitis loss of myelin basic protein was co-extensive with the cellular infiltrate, and myelin basic protein was present only immediately adjacent to the outer rim of perivascular cells. Cells containing myelin basic protein were very rare in the lesions of experimental allergic encephalomyelitis, compared to the lesions of multiple sclerosis. Although the initial event for damage and removal of myelin basic protein remains unidentified, there is yet no convincing evidence that the mechanism for loss of myelin basic protein in multiple sclerosis is a direct result of either cell-mediated demyelination or antibody to intact myelin basic protein.

Antibodies to intact myelin basic protein are uncommonly found in serum or cerebrospinal fluid of patients with multiple sclerosis, and cell-bound antibody to intact myelin basic protein has not been detected in lesions of multiple sclerosis. Degradation of myelin basic protein may be brought about by the action of acid proteinase which is increased in plaques of multiple sclerosis. This alone, however, does not account for the differences in distribution of myelin basic protein in experimental allergic encephalomyelitis and multiple sclerosis, because acid proteinase is also increased in the brains of animals with experimental allergic encephalomyelitis. The results of his study suggest differences between multiple sclerosis and acute experimental allergic encephalomyelitis in both the pattern of removal of myelin basic protein during myelinolysis and the subsequent disposal of myelin basic protein.

In another study, Gutstein and Cohen[18] compared the cerebrospinal fluid of sheep with experimental allergic encephalomyelitis and that of patients with multiple sclerosis. In the former they detected antibody to myelin basic protein as well as excess free myelin basic protein. In multiple sclerosis, only free myelin basic protein could be found. They also report that in experimental allergic encephalomyelitis, myelin basic protein antibodies entered cerebrospinal fluid from serum by passive transfer, a mechanism they propose as an explanation for the presence of viral antibodies in the cerebrospinal fluid in multiple sclerosis. They caution that the use of experimental allergic encephalomyelitis as a model for multiple sclerosis should be carefully questioned. On the basis of his review of tissue culture studies of demyelinating disease, Seil[43] stated that the demyelinating factor in mul-

tiple sclerosis is induced by a different antigen than that which induces the antibody in experimental allergic encephalomyelitis and may therefore have a different meaning with regard to pathogenesis. He concluded that result of studies of serum antimyelin factors in experimental allergic encephalomyelitis cannot be extrapolated to multiple sclerosis, and the relevance of serum antimyelin factors to underlying causative mechanisms in multiple sclerosis has not been established.

The problem remains unsolved. However, the suggestion has been made that the initiating mechanisms in multiple sclerosis and in experimental allergic encephalomyelitis may be identical, but that the propagative mechanism underlying multiple sclerosis is lacking in experimental allergic encephalomyelitis; thus, the latter would indeed be useful as a model for initiating a systemic immunologic disturbance which, in some individuals, would result in nonspecific pathologic changes (including alteration of the blood brain barrier); in others it would produce the classical perivascular demyelination, while in still others would trigger a special mechanism that would form plaques of multiple sclerosis. A major obstacle to this hypothesis has been the generally accepted statement that the blood-brain barrier is intact in multiple sclerosis. This concept, already questioned previously[34] has now clearly become untenable in view of the fact that in certain patients with multiple sclerosis, radionuclide brain scans and contrast-enhanced computed tomography reveal significant alterations of the blood-brain barrier. The knowledge that an alteration of the blood-brain barrier indeed occurs in multiple sclerosis at some time and persists for various periods of time, also gives credence to the belief that multiple sclerosis should no longer be considered to be a disease restricted to the nervous system, but rather a systemic illness which manifests itself exclusively by producing lesions in the central nervous system.

Epidemiology and Genetics

Kurtzke[21] has unequivocally stated that multiple sclerosis is a geographically related disease and thus can be thought of as an acquired environmental (exogenous) illness, and that all the epidemiologic information would be most easily explained if multiple sclerosis were an infectious (viral) illness with prolonged latency. In support of this, among other arguments, he alludes to the curious sudden "epidemic" of the disease in the Faroe Islands which would appear to have followed the presence of British troops during World War II. This geographic explanation may be too simplistic since data referring to latitude and longitude can just as well be interpreted as denoting a predisposition among populations of predominantly Germanic (including Anglo-Saxon and Scandinavian origin). The important of environmental factors, confirmed by immigration studies,[35] cannot be denigrated but will have to be correlated with genetic (histocompatibility) studies. Both exogenous (probably infectious) and endogenous (immunogenetic) factors will have to be considered to understand the geographic distribution of multiple sclerosis.

A great deal of interest has been generated by the reports of Cook et al.[10] and others which purport to establish an association between multiple sclerosis and close contacts with household pets, small dogs in particular. Other investigators have not found such association, and Sylwester and Poser[44] were able to demonstrate a similar statistically significant association between the disease and exposure to cows and/or chickens. Furthermore, they also pointed out that any risk factor associated with exposure to dogs in their study could be ascribed to the fact that individuals who have cows and/or chickens also are more likely to have dogs. The implication of the association with dogs is that canine distemper virus (a relative of measles) may play a role in the etiology of the disease. A study by Nathanson et al.[30] of multiple sclerosis and canine distemper in Iceland conclusively showed that multiple sclerosis has occurred in that country in regions in which distemper has been essentially absent for close to 70 years. Thus, Iceland is a country with a very high prevalence of multiple sclerosis in the virtual absence of distemper. In addition, the almost total elimination of dogs in Reykjavik for at least 50 years has not prevented a high prevalence of multiple sclerosis.

Most of the published studies of potential risk factors exemplify the dangers of playing statistical games with data obtained retrospectively from small numbers of subjects. Such studies are designed to test a particular hypothesis and collect only information which the investigator believes to be relevant. Further confusion is created by failing to distinguish between causative and precipitating events. What is yet to be accomplished is a collaborative effort, involving large numbers of patients with multiple sclerosis and well selected controls, including siblings and coeval non-siblings exposed to similar environmental factors, investigating all possible risk factors.

Histocompatibility studies of patients with multiple sclerosis have opened up perhaps the most important and exciting avenue of research in this disease in many years. The original reports by a number of investigators of a significant increased incidence of the histocompatibility antigens A3, B7, and in particular, DW2 in western European and North American Caucasians strongly suggested that a genetically determined factor may play an important role in the pathogenesis of multiple sclerosis.[35] As more populations were studied, however, it became quite clear that the association with these particular antigens was quite inconsistent (Table 1). An additional important finding relates to the statistically significant decreased incidence of certain histocompatibility antigens which suggests the possible existence of protective genetic factors as well.

The relationship between histocompatibility antigens and the presence of elevated viral antibody titers[2, 14, 32] offers a potentially fruitful area of investigation for the purpose of establishing the pathogenic significance, if any, of the many immunologic alterations that have been reported in multiple sclerosis.

The hope of identifying groups and individuals prone to develop multiple sclerosis on the basis of these promising studies has yet to be

Table 1. *Statistical Significance of Histocompatibility Antigens in Patients with Multiple Sclerosis*

GROUP	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
COUNTRY	USA	USA	USA	CAN	DENM	NORW	GER	AUST	ISRL	IRAN	JAPAN
NO. OF PATIENTS	135	330	56	224	209	46	1000	50	197	35	41
ANTIGEN											
A1	−.025		0		−.05	−.05	.001	0	0	0	0
A3	0	0	+.005	+.01	+.01	0	+.001	+.01	0	+.001	0
A10	0		0	0	0		0		+.02	−	0
A11	0		0	0	0		0	0	+.04	+.001	0
AW19	−.025		0	0	0		0	0	0	0	0
B7	+.05	0	+.025	+.001	+.001	+.05	+.001	+.005	0	+.005	0
B8	0		+.05	0	0	0	0	0	0	0	+
B12	−.05		0	.005	−.05	-.05	−.001	0	0	0	--
B18	0			+.005	0	0	0	0	0	0	0
BW15	0		0	0	0	0	−.001	0	0		0
BW17	0			0	−.01	0	0	−.05	0	0	0
BW22	0		0	0	−.05	0	0	0	0	0	0
BW35	+.005			0		0			0	0	0
BW40	−.01			0		0			+.001	0	0
DW2		+.00001			+.000002	+.001		+.0001	0		0

I US JNSci 34:287,77
II US Tiss Ant 9:54,77
III US JNSci 22:419,74
IV Canada JNSci 32:371,77
V Denmark Transpl Rev 22:148,75
VI Norway JNSci 32:187,77
VII Germany Cit.V
VIII Australia JNSci 32:153,77
IX Israel Tiss Ant 10:291,77
X Iran JNNsPsy 41:699,78
XI Japan Tiss Ant 10:191,77

realized. In an extremely important study, Eldridge et al.[11] investigated seven families with two or more first degree relatives affected with multiple sclerosis and reviewed 28 similar families reported elsewhere. No consistent segregation of HLA type was noted between affected and unaffected individuals in these families. They concluded that there is not a single mapping in the genetic complex which predisposes to multiple sclerosis. In none of the seven families was there a specific haplotype which occurred only in affected members. There seems to be little or no relationship between genes at the HLA-A or B locus or DW status and the course of the disease. No particular relationships between HLA type or DW2 phenotype and measles antibody titer was observed.

Several conclusions can be drawn from the many studies of the HLA system in multiple sclerosis: there may well be a genetic factor, located in the vicinity of some of the loci on the sixth chromosome, but these loci are quite different in various populations. Secondly, a single specific genetic association is unlikely but it is probable that the associations are secondary effects of linkage dysequilibrium, a tendency of certain alleles of linked but different loci to occur in association; what may be genetically determined is an abnormality of antibody production.[9] Identification of an individual's haplotype or genotype even in an affected family has no predictive value whatsoever. It is then the combination of genetic factors and exposure to a variety of viral agents which probably determines the risk of multiple sclerosis.

DIAGNOSTIC METHODS

Cerebrospinal Fluid

Cohen et al.,[7] using a radioimmunoassay of myelin basic protein, reported having found a direct correlation between the levels of myelin basic protein in cerebrospinal fluid and the clinically determined activity of the disease. False-positive results included other conditions characterized by destruction of myelin. They claim, however, that the material is found only very rarely in patients with strokes. A number of authors[1] have confirmed the value of agarose electrophoresis for the demonstration of oligoclonal IgG bands which can be found in over 90 per cent of patients with multiple sclerosis. Unfortunately, the rate of false-positive results can be as high as 40 per cent and thus the test is hardly specific for the disease. The significance of these oligoclonal bands remains obscure. Because of the technical difficulties relating to this procedure, it has not yet gained wide clinical acceptance. The determination of cerebrospinal fluid IgG by radioimmunoassay and other methods remains the mainstay of cerebrospinal fluid diagnosis, although its overall accuracy in the routine clinical laboratory is approximately 50 per cent. Schmidt et al.[40] have once again demonstrated that there is no correlation between the level of cerebrospinal fluid IgG and age, duration of illness, clinical activity, extent of plaques, or

gravity of the illness. Williams et al.[48] and others have now shown that in a significant number of patients there is elevation of the cerebrospinal fluid IgM level, without correlation with the IgG level. At the present time, in terms of attempting to determine the level of activity of the disease, the only reliable indicator is the presence of cerebrospinal fluid leukocytosis.

Clinical Neurophysiology

An increasing number of reports have underlined the value of neurophysiological studies, in particular visual evoked potentials to both flash and pattern reversal stimulation, in confirming the presence of lesions in the optic nerves, and more important, in demonstrating the existence of hitherto unsuspected or asymptomatic lesions in the visual system. Halliday et al.,[19] using a checkerboard pattern of light and dark squares reversed at a frequency of 2 per second, found abnormalities in 86 per cent of patients with normal optic discs and without a history of optic neuropathy. McSherry and O'Brien[27] have developed a technique for demonstrating the presence of unsuspected retrochiasmatic lesions in patients with multiple sclerosis by means of visual evoked responses. Bynke et al.[4] demonstrated that 76 per cent of 25 patients with myelopathy of unknown etiology and without subjective symptoms of central nervous system involvement outside the spinal cord had increased visual evoked potential latencies. Lowitzsch et al.[24] measured the optically and electrically evoked Kimura blink reflexes in 107 patients with multiple sclerosis. All patients with mesencephalic lesions had delayed responses of the optically evoked reflex and 74 per cent of these patients had delayed latency of the components of the electrically evoked blink reflex. In addition, 18 patients without brain stem signs had a delay of the blink reflex.

Robinson and Rudge[39] measured the brain stem auditory evoked responses and found them to be abnormal in half their patients with multiple sclerosis without clinically detectable brain stem signs or symptoms. Mastaglia et al.[26] found that 56 per cent of their patients had abnormal somatosensory evoked responses and of these at least 19 (41 per cent) were without clinical sensory symptoms or signs. Furthermore, 48 per cent of 54 patients with multiple sclerosis had abnormal horizontal saccadic eye movement velocity.

The neurophysiologic studies serve the useful purpose of documenting the existence of multiple lesions and confirming or denying the validity of past events and current symptoms. The introduction of these procedures to clinical practice must be considered as one of the most important advances in the diagnosis of multiple sclerosis and has allowed clinicians to move patients from the possible and probable categories into the definite group. In some instances, these tests also provide means of determining if the appearance of new or recurrent symptoms represent a true exacerbation of the disease, a hysterical manifestation or a psychologically induced recall phenomenon.[36] They also at times provide objective evidence of improvement.

Neuroradiology

The technetium 99 radionuclide brain scan can demonstrate only lesions with a diameter of at least 1.5 cm and the yield of the procedure is relatively small. In some instances, some correlation has been obtained between the symptoms and the brain scan, providing objective evidence for exacerbation.[29]

Several papers have also emphasized the value of computed tomography (CT) for both the diagnosis of the disease and the evaluation of its activity. Some of these data, however, must be interpreted with care. Wuthrich et al.[50] examined 60 patients with multiple sclerosis and found that only in 31 were the CT scans normal; atrophy was a common finding but is not specific enough to be of significant value; unequivocal foci were present in 5 and equivocal foci were present in 15 of their cases. Cala et al.[5] examined 100 patients with established or suspected multiple sclerosis with CT scanning. They found areas compatible with demyelinating lesions in the white matter of the cerebral hemisphere and brain stem in 47 per cent. These lesions of the hemisphere were commonly multiple, typically situated in the deep white matter and periventricular regions, and were often asymptomatic. They make the important point that lesions in spinal cord, brain stem, and cerebellum, being usually quite small, can be identified only by study of the computer printout. Computed tomography can be of great value in demonstrating the multiplicity of lesions in patients with possible or probable multiple sclerosis. The test, however, is not as sensitive as clinical neurophysiologic studies and is also considerably more expensive.

Of perhaps even greater theoretical importance are the studies of contrast-enhanced computed tomography. Sears et al.[42] reported a series of four patients in whom lesions were demonstrated by contrast enhancement at the time of clinical exacerbations. Furthermore, they showed that corticosteroid therapy reduced the intensity of enhancement. They believe that the basis for this phenomenon is a transient alteration of vascular permeability, and that corticosteroid therapy reestablishes the integrity of the blood-brain barrier. One of their cases is of particular interest in that the focal enhancement occurred twelve hours prior to the clinical manifestations of an exacerbation.

Both radionuclide studies and contrast-enhanced computed tomography studies re-emphasize the need to consider that a transient alteration of blood-brain barrier permeability may precede the appearance of clinical symptoms. These studies would also suggest that improvement following ACTH or corticosteroid therapy may be related to the same phenomenon. Finally, they put credence in the suggestion made that the best time to look for manifestations of the pathogenetic mechanism of multiple sclerosis is shortly before the onset of clinical symptoms.[34] Careful analysis of several published cases of multiple sclerosis with lesions demonstrated by radionuclide or enhanced CT scanning, presumably showing disease activity, reveals poor, possibly even coincidental clinico-anatomical correlation with concurrent symptomatology. This troubling observation raises difficult questions in regard to the pathogenetic mechanism of the clinical exacerbation. In addition to

the diagnostic procedures already mentioned, examination of the patient for monocular color blindness (usually of the red-green type) with pseudo-isochromatic Ishihara or AO plates can be quite useful, as is the use of the hot bath test (water temperature at 40° C). This latter procedure may bring out signs and symptoms which have previously not been experienced by the patient, or may reproduce symptoms reported by the patient but not objectively confirmed.

CLINICAL ASPECTS

The classical clinical notion that the course of multiple sclerosis characterized by remissions and exacerbations closely reflects the underlying pathological changes needs closer examination. While it has usually been assumed that new plaques have developed in the patient who suddenly experiences symptoms, physiological, radiological, and pathological studies reveal that asymptomatic lesions may have been present for quite some time. Symptoms and signs of multiple sclerosis may indeed result from the formation of plaques, but it is now clearly understood that they may also result from physiologic alterations (e.g., heat, calcium concentration) affecting previously existing plaques.[35] In addition, other mechanisms must be considered: since symptoms and signs may be the result of swelling rather than destruction of myelin, it is conceivable that when the edema subsides, the myelin does not revert to its normal state, and thus may be more vulnerable to these physiological alterations. Recurrence of edema in the same location is still another possibility, as is enlargement of a previously existing plaque. The occurrence of a new lesion at another level of one of the long tracts may also mimic a previously experienced symptom. Furthermore, while the exact pathogenetic relationship between emotional stress and physical trauma is poorly understood, the association of these events with acute exacerbations or appearance of new symptoms is well documented. It is not farfetched to suggest that some still not understood physiological alteration affects conductivity in a manner similar to changes in temperature or calcium concentration: the phenomenon of such psychologically induced recall needs further study.

Thygesen[46] in his review of 105 attacks of the disease in 60 patients pointed out that a new symptom suggestive of a new plaque occurred in only 19 per cent of these attacks. An attack often affects precisely one previously damaged site of the central nervous system and is a true copy of previously remitted symptoms. It would seem that clinical exacerbations can with equal probability represent either physiologic alterations or evidence of the production of new plaques, or expansion or reactivation of old ones. Many patients with multiple sclerosis have admitted, upon close questioning, that certain symptoms never actually disappear, but they get accustomed to them so that they are ignored until some external event brings them to mind.[36] In other words, this suggests that clinical observation provides only a very incomplete and inaccurate reflection of the progression of the disease in terms of formation of new plaques. Clinical evaluation of degree of activity of the underlying demyelinizing process is totally in-

adequate and particularly burdensome when trying to evaluate the results of therapeutic regimens. Measurements of evoked responses and to a lesser extent radionuclide and contrast-enhanced CT studies will prove to be of considerable help in this regard.

The notorious lack of clinicopathologic correlation in multiple sclerosis is best exemplified by our continued inability to detect lesions in the subcortical white matter such as the classical periventricular plaque. It is well known that even large plaques are found at autopsy in patients who have never had neurologic symptoms.[17, 35] It must also be pointed out that it may be quite wrong to assume that the bilateral Babinski signs and nystagmus found in a patient who presents with numbness of the left arm all occurred simultaneously. Our understanding of the pathophysiological changes which result from the presence of demyelinizing lesions is still too incomplete to allow for the establishment of chronologic relationships between symptoms and their underlying lesions. This problem assumes great importance in not only gauging the overall progression of the disease but also in evaluating the possible relationship existing between external factors such as emotional stress and/or physical trauma and the occurrence of signs and symptoms. That these represent precipitating events is undeniable; that they are responsible for plaque formation is highly unlikely.[36] Finally, the slow progression of symptoms and signs may represent nothing more than the results of the reparative gliosis secondary to the inflammatory reaction to the myelinoclastic process.

Mention should also be made of the value of psychological evaluation. Peyser et al.[33] have demonstrated the presence of unsuspected significant cognitive impairment in 49 per cent of patients judged by the neurologist to be mentally intact. This impairment is unrelated to the severity of overall neurologic involvement but appear to correlate best with a history or presence of involvement of the visual system; the visual involvement, however, is not a factor in the cognitive impairment. These findings suggest that cognitive impairment may represent the clinical manifestations of some of the subcortical white matter plaques which are otherwise asymptomatic. These evaluations also may provide useful guidelines for the physician in the overall management of the patient, including the recognition that psychological characteristics may influence the course of the illness and the occurrence of exacerbations.

TREATMENT

Nearly all therapeutic regimens have been based upon the belief that multiple sclerosis results from a hyperimmune state and a number of immunosuppressive agents and measures have been utilized. Ellison and Meyers[12] reviewed the use of systemic nonspecific immunosuppressive agents including cyclophosphamide, azathioprine and levamisole: frequency of relapse, rate of progression, and cerebrospinal fluid IgG may be decreased, at least temporarily, in some patients treated with these agents; the few controlled studies of immunosuppressive therapy show less apparent benefit than the uncontrolled

studies but treatment regimens have not been directly comparable. In general, the dosages used and the duration of follow-up have been inadequate. They suggest that routine use of immunosuppressants is not warranted at this time. Further, it raises serious ethical problems. While the short-term after-effects are well documented, patients have not been followed for lengths of time adequate enough to detect increased malignancy or other and unsuspected complications. No laboratory test seems completely predictive of efficacy.

Treatment based upon the concept of multiple sclerosis as an immunodeficiency state, using transfer factor, has proved to be valueless.[15]

Other forms of therapy based upon less convincing rationales and with inconclusive and contradictory results have included linoleic acid, tryptophan, plasmapheresis, human myelin basic protein, hyperbaric oxygen, anti-thymic globulin, total body x-irradiation, and so forth.

In spite of the fact that their use remains extremely controversial, many clinicians continue to administer different corticosteroids or ACTH for the treatment of acute symptoms. The general belief, albeit anecdotal, is that these drugs do indeed shorten the course of the exacerbation and afford relief of symptoms. There appears to be considerable variation in individual patients in their response to either ACTH or corticosteroids. Similarly, some patients will have dramatic response to one corticosteroid while others will respond to another, or to cosyntropin and not to ACTH. The only rationale that can be invoked for their use is as anti-edema and anti-inflammatory agents, and possibly as stabilizers of the capillary membrane. It is possible that myelin edema may respond to ACTH or corticosteroids but myelin destruction does not. In regard to symptomatic treatment, dantrolene and baclofen, the latter in particular,[13] have been of some value in the relief of spasticity and its concomitant symptoms such as flexor spasm, clonus, and resistance to passive movement. Unfortunately, these drugs may cause gastrointestinal disturbances, and interference with ambulation in those patients who need a certain amount of spasticity in order to lock hip and knee joints.

The control of bladder problems such as frequency, urgency, and stress incontinence remains one of the most important aspects of long-term management. The judicious use of propantheline bromide (probanthine) or drugs with a similar parasympatholytic effect, will provide the patient with relief for several hours. External sphincterotomy will make the use of a Texas catheter and leg urinal comfortable for a male patient and will avoid the need for repeated self-catheterization.

In general, patients who can be demonstrated, by hot bath tests or by history, to be sensitive to heat should avoid hot showers or baths and prolonged exposure to the sun. The installation of air conditioning units in the patient's home may maintain him or her in a functional state during hot summer weather.

The placebo effect of any kind of therapeutic regimen, of simple rest at home, or of hospitalization and removal from the stresses and strains of daily life must always be considered, since in some patients exacerbations may represent a psychophysiological phenomenon. It

should also be pointed out that patients may be highly motivated by an enthusiastic investigator using a specific form of treatment, who thus provides the patient with considerable attention and who may unwittingly reinforce this placebo effect. Many of the proposed therapeutic regimens are designed to test a particular etiologic or pathogenetic hypothesis; until we have a better understanding of the pathogenesis of multiple sclerosis, such hypothesis-testing should be entered upon only with extreme care and detailed preparation,[41] and with the full realization that the mechanics of treatment, i.e., the placebo effect, may be more beneficial to the patient than the treatment itself.

REFERENCES

1. Antel, J. P., Weinrich, M., and Arnason, B. G. W.: Mitogen responsiveness and suppressor cell function in multiple sclerosis. Neurology, *28*:999–1003, 1978.
2. Arnason, B. G. W., et al.: Histocompatibility types and measles antibodies in multiple sclerosis and optic neuritis. J. Neurol. Sci., *22*:419–428, 1974.
3. Burks, J. S.: A possible corona virus isolation from MS autopsy material. NMSS Med. Dept. Memo No.97–78, Sept, 8, 1978.
4. Bynke, H., Olsson, J. E., and Rosen, I.: Diagnostic value of visual evoked response, clinical eye examination and CSF analysis in chronic myelopathy. Acta Neurol. Scand., *56*:55–69, 1977.
5. Cala, L. A., Mastaglia, F. L., and Black, J. L.: Computerized tomography of brain and optic nerve in multiple sclerosis. J. Neurol. Sci., *36*:411–426, 1978.
6. Carp, R., Merz, G., and Licursi, P.: A non-cytopathic infectious agent associated with MS material. Neurology, *25*:492–493, 1975.
7. Cohen, S. R., Herndon, R. M., and McKhann, G. M.: Radioimmunoassay of myelin basic protein in spinal fluid. New Engl. J. Med., *295*:1455–1457, 1976.
8. Cohn, H., et al.: Appraisal of the PAM cell effect as a diagnostic test for multiple sclerosis. Ann. Neurol., *3*:400–402, 1978.
9. Compston, A.: HLA and neurologic disease. Neurology, *28*:413–414, 1978.
10. Cook, S., et al.: Further evidence of a possible association between house dogs and multiple sclerosis. Ann. Neurol., *3*:141–143, 1978.
11. Eldridge, R., McFarland, H., and Sever, J.: Familial multiple sclerosis: clinical histocompatibility and viral serological studies. Ann. Neurol., *3*:72–80, 1978.
12. Ellison, G. W., and Myers, L. W.: A review of systemic nonspecific immunosuppressive treatment of multiple sclerosis. Neurology, *28*(2):132–139, 1978.
13. Feldman, R., et al.: Baclofen for spasticity in multiple sclerosis. Neurology, *28*:1094–1098, 1978.
14. Fewster, M. E., et al.: Histocompatibility types and measles antibodies in multiple sclerosis. J. Neurol. Sci., *34*:287–296, 1977.
15. Fog, T., et al.: Long-term transfer factor treatment for multiple sclerosis. Lancet, *1*:851–853, 1978.
16. Fuccillo, D. A., et al.: Multiple sclerosis: Cellular and humoral immune responses to several viruses. Neurology, *28*:613–615, 1978.
17. Ghatak, N. R., et al.: Asymptomatic demyelinated plaques in the spinal cord. Arch. Neurol., *30*:484–486, 1974.
18. Gutstein, H. S., and Cohen, S. R.: Spinal fluid differences in experimental allergic encephalomyelitis and multiple sclerosis. Science, *199*:301–303, 1978.
19. Halliday, A., McDonald, W., and Mushin, J.: Visual evoked response in diagnosis of multiple sclerosis. Brit. Med. J., *4*:661–664, 1973.
20. Henle, G., et al.: Multiple sclerosis associated agent. Infect. Immun., *12*:1367–1374, 1975.
21. Kurtzke, J. F.: Geography in multiple sclerosis. J. Neurol., *215*:1–26, 1977.
22. Levy, N., Auerbach, P., and Hayes, E.: A blood test for multiple sclerosis based on the adherence of lymphocytes to measles infected cells. New Eng. J. Med., *294*:1423–1427, 1976.
23. Lisak, R. P., et al.: Cell mediated immunity to measles, myelin basic protein, and central nervous system extract in multiple sclerosis. Neurology, *28*:798–803, 1978.
24. Lowitzsch, K., et al.: Visual evoked responses and blink reflexes in assessment of MS diagnosis. J. Neurol., *213*:117–32, 1976.

25. Madden, D. L., et al.: Multiple sclerosis associated agent (MSAA): Failure to confirm an association with multiple sclerosis. Neurology, 28:295–299, 1978.
26. Mastaglia, F., et al.: Evoked potentials, saccadic velocities, and computerized tomography in diagnosis of multiple sclerosis. Brit. Med. J., *1*:1315–1317, 1977.
27. McSherry, J., and O'Brien, P.: Visual evoked responses in multiple sclerosis. In press.
28. Mitchell, D. N., et al.: Isolation of an infectious agent from bone marrows of patients with multiple sclerosis. Lancet, 2:387–391, 1978.
29. Murray, S., and Veidlinger, O. F.: Serial radionuclide scans in multiple sclerosis. Can. J. Neurol. Sci., 5:321–323, 1978.
30. Nathanson, N., Paulsson, P., and Gudmundsson, G.: Multiple sclerosis and canine distemper in Iceland. Lancet, 2:1127–1129, 1978.
31. Offner, H., Konat, G., and Clausen, J.: A blood test for multiple sclerosis. New Engl. J. Med., 296:451–454, 1977.
32. Paty, D. W., et al.: HLA in multiple sclerosis. Relationship to measles antibody, mitogen responsiveness and clinical course. J. Neurol., Sci., 32:371–379, 1977.
33. Peyser, J., Edwards, K., and Poser, C.: Cognitive function in multiple sclerosis patients. Arch Neurol., in press.
34. Poser, C.: Multiple Sclerosis. *In* Tower, D., ed.: The Nervous System. New York, Raven Press, 1975, Vol. 2, p. 337–345.
35. Poser, C.: Multiple Sclerosis. *In* Baker, A., and Baker, L., ed.: Clinical Neurology. New York, Harper and Row, 1978, Vol. 2, Chap. 25, p. 1–70.
36. Poser, C. M.: Stress, trauma and multiple sclerosis. Bull. Am. Acad. Psychiat. Law, in press.
37. Poser, C., Roman, G., and Emery, E.: Recurrent disseminated vasculomyelinopathy. Arch. Neurol., 35:166–170, 1978.
38. Raine, C. S., et al.: Immunocytochemical studies for the localization of measles antigens in multiple sclerosis plaques and measles virus-infected CNS tissue. J. Neurol. Sci., 33:13–20, 1977.
39. Robinson, K., and Rudge, P.: Auditory evoked response in multiple sclerosis. Lancet, *1*:1164–1166, 1975.
40. Schmidt, R., Rieder, H. P., and Wutrich, R.: The course of multiple sclerosis cases with extremely high γ-globulin values in the cerebrospinal fluid. Eur. Neurol., *15*:241–248, 1977.
41. Schumacher, G.: Critique of experimental trials of therapy in multiple sclerosis. Neurology, 24:1010–1014, 1974.
42. Sears, E. S., Tindall, R. S. A., and Zarnow, H.: Active multiple sclerosis: enhanced computerized tomographic imaging lesions and the effect of corticosteroids. Arch. Neurol., 35:426–434, 1978.
43. Seil, F. J.: Tissue culture studies of demyelinating disease: a critical review. Ann. Neurol., 2:345–355, 1977.
44. Sylwester, D., and Poser, C.: Multiple sclerosis, domestic animals and household pets. Ann. Neurol., 5:207–208, 1979.
45. Symington, G. R., and Mackay, I. R.: Cell-mediated immunity to measles virus in multiple sclerosis: correlation with disability. Neurology, 28:109–112, 1978.
46. Thygesen, P.: The course of disseminated sclerosis: A close-up of 105 attacks. Copenhagen, Rosenkilde and Bagger, 1953, pp. 71–93, 141–142.
47. Whitaker, J. N.: The distribution of myelin basic protein in central nervous system lesions of multiple sclerosis and acute experimental allergic encephalomyelitis. Ann. Neurol., 3:291–298, 1978.
48. Williams, A. C., et al.: Increased CSF IgM in multiple sclerosis. Neurology, 28:996–998, 1978.
49. Wisniewski, H. M., and Keith, A. B.: Chronic relapsing experimental allergic encephalomyelitis: An experimental model of multiple sclerosis. Ann. Neurol., *1*:144–148, 1977.
50. Wuthrich, R., et al.: CT scanning in demyelinating disease. *In* Laubsch and Razner, eds.: *In* Cranial Computerized Tomography, Springer Verlag, 1976, pp. 239–243.

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Current Concepts of Pathogenesis and Treatment of Myasthenia Gravis

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Myasthenia gravis is an autoimmune disease of man characterized by remitting and relapsing muscle weakness and fatigability which results from a defect in neuromuscular transmission. Although the etiology and pathogenesis of myasthenia gravis are incompletely understood, extensive studies of the acetylcholine receptor and the immune system have clarified many features of this disorder. The defect in neuromuscular transmission has been localized to the skeletal muscle motor endplates which possess morphological,[22] electrophysiological,[4] and biochemical abnormalities.[18, 23, 31] These changes in the postsynaptic membranes of skeletal muscle are thought to be due to the presence of humoral antibodies that bind to nicotinic acetylcholine receptors.[6] These acetylcholine receptor antibodies can be detected in the serum of most patients with myasthenia gravis,[9, 32] and IgG can be detected on motor endplates of patients' skeletal muscle.[21]

This view of myasthenia gravis as a postsynaptic disease of autoimmune origins poses several questions: (1) What is the mechanism by which antibodies directed against the acetylcholine receptor produce a defect in neuromuscular transmission? (2) Are the receptor antibodies both necessary and sufficient to produce clinical disease? (3) How do such antibodies arise? (4) What are the therapeutic implications of these antibodies in myasthenia gravis? This review will focus on these questions. There are several excellent reviews of more clinical aspects of myasthenia gravis[35] and current therapy.[37]

The Autoimmune Response and the Neuromuscular Transmission Defect

The apparent similarity of myasthenia gravis to curare poisoning led to the suggestion that myasthenia gravis was due to a circulating

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"curare-like" substance. The weakness present in infants of myasthenic mothers reinforced this notion by suggesting that some "myasthenia-producing" factor was transferred from the mother to her infant. The association of myasthenia gravis with abnormalities of the thymus and other autoimmune diseases led to the proposal that this factor involved an autoimmune response. However, no such factor was identified until the discovery of circulating antibody that binds to acetylcholine receptors in patients with myasthenia gravis.[6]

It has now been established that there is both a humoral[6, 9, 32] and a cellular[2] immune response directed against acetylcholine receptors in most patients with myasthenia gravis. Humoral acetylcholine receptor antibodies appear to be most responsible for the neuromuscular transmission defect in patients with myasthenia gravis. These antibodies bind to acetylcholine receptors and can be detected in the sera in 70 to 90 per cent of patients with myasthenia gravis.[9, 32] Furthermore, immunoglobulins isolated from the sera of patients with myasthenia gravis cause weakness and depletion of acetylcholine receptors when injected into animals.[42] Additional evidence for the involvement of a humoral mechanism is the localization of IgG and C_3 component of complement at motor endplates of patients with myasthenia gravis using immunohistochemical techniques.[21] The sole support for a cell-mediated attack on the neuromuscular junction is the presence of cellular infiltrates (lymphorrhages) in muscle of patients with myasthenia gravis, but they are not seen in the region of the endplate.

Role of Receptor Antibodies in Myasthenia Gravis

Acetylcholine receptor antibodies are believed to initiate events that produce a decreased concentration of functional acetylcholine receptors in the motor endplates of skeletal muscles in myasthenia gravis. There are several explanations of how this might occur: (1) acetylcholine receptor antibodies could block the access of acetylcholine to the acetylcholine receptor, (2) the binding of antibodies could stimulate lysis of the postsynaptic membranes, (3) acetylcholine receptor degradation could be accelerated, or (4) acetylcholine receptor synthesis could be inhibited.

Although receptor antibodies may block access of alpha-bungarotoxin in the acetycholine receptor,[6, 10, 13] there has been no direct confirmation that acetylcholine receptor antibodies block the access of acetylcholine to the acetylcholine receptor in patients with myasthenia gravis. Short-term exposure of neuromuscular junctions to myasthenic serum or immunoglobulins does not alter neuromuscular transmission in vitro.[3] These antibodies appear to bind to a site on the acetylcholine receptor other than the acetylcholine binding site since the binding of antibody and alpha-bungarotoxin to the receptor is noncompetitive.[7] Thus, the blockade by antibody is probably one of steric hindrance. It has been possible to demonstrate in myotube cultures that blockade of alpha-bungarotoxin binding does not correlate with blockade of acetylcholine access to acetylcholine receptors.[3]

Morphologic studies of the neuromuscular junctions in patients

with myasthenia gravis are consistent with the interpretation that antibodies induce breakdown and extrusion of postsynaptic membranes into the intersynaptic cleft.[22] By ultrastructural techniques, IgG and the C_3 component of complement can be localized both to the motor endplate and membrane debris in the synaptic cleft in myasthenic intercostal specimens. These data suggest that membrane is lysed in a complement-dependent reaction resulting in a loss of acetylcholine receptors in the shed membrane fragments.

An alternative hypothesis suggests that acetylcholine receptors are decreased by a process of accelerated endocytosis analogous to antigenic modulation in lymphocytes. Several laboratories have now demonstrated accelerated degradation of acetylcholine receptors produced by myasthenia gravis immunoglobulins in myotube cultures[8, 10, 26, 29] and in adult synapses.[40] Devreotes and Fambrough[17] demonstrated that acetylcholine receptor turnover could be monitored in myotube culture by measuring the disappearance of alpha-bungarotoxin binding sites. The addition of serum or immunoglobulins to the culture medium increases the rate of disappearance of acetylcholine receptors.[10, 26, 29] In our own studies, the half-life of acetylcholine receptors decreased from 18 hours to 6 hours when measured by toxin-binding[10] or electrophysiologic techniques[8] (Table 1). The half-life of junctional acetylcholine receptors in adult synapses is normally much longer than in myotube cultures, but degradation of junctional receptors is accelerated by myasthenia gravis immunoglobulin.[40]

We have also determined that incorporation of new acetylcholine receptors into myotube membranes is decreased when cultures are incubated with myasthenia gravis immunoglobulin or sera[11] (Table 2). These studies measured incorporation of new receptors by the methods of Deverotes and Fambrough.[17] If the cultures are washed after incubation with myasthenia gravis immunoglobulins, and incubation is continued for additional periods of time, a normal rate of receptor incorporation returns within 2 hours. Our data suggest that the decreased incorporation of new receptors is caused by decreased synthe-

Table 1. *Effect of Myasthenic or Normal Sera on the Decay of Labeled Acetylcholine Receptor*

EXPERIMENT	NORMAL SERA Rate Constant hr^{-1}	NORMAL SERA $T_{1/2}$ hr	MYASTHENIC SERA Rate Constant hr^{-1}	MYASTHENIC SERA $T_{1/2}$ hr
1	–	–	.123	5.6
2 (post-label)	–	–	.087	8.0
3	.033	21.0	.156	4.4
4 (post-label)	–	–	.091	7.6
5	.044	15.8	.200	3.5
6	.037	18.7	.087	7.9
7	.036	19.3	.065	10.7
Mean ± SEM	.0375 ± .002	18.5 hr	.115±.018	6 hr

In each experiment, duplicate cultures were incubated for varying time periods.

Table 2. *Rate of Appearance of Acetylcholine Receptors in Surface Membrane in Presence of Normal or Myasthenia Gravis Globulin*

	NORMAL	MYASTHENIA GRAVIS
0–24 H	530 ± 38	206 ± 91
24–48 H	503 ± 115	473 ± 45

Values are mean ± standard deviation in cpm/hr/10^6 cells. The rate (K_s) was determined by measuring the number of receptors accumulated from 0–24 hour period and correcting for degradation during the same period. At 24 H the cultures were washed and fed with normal media. Thus, 24–48 H represents the recovery period.

sis of acetylcholine receptors, as well as decreased insertion of new receptors into the surface membrane. In cultures incubated with normal media, incorporation of new receptors is essentially equal to synthesis of receptors.[33]

An additional mechanism by which acetylcholine receptor antibodies might produce a defect in neuromuscular transmission is alteration of the ion conductance changes that occur after acetylcholine binds to the acetylcholine receptor. However, motor endplates in myasthenia gravis do not show altered ion channel properties.[15]

In summary, humoral antibodies could produce decreased concentration of acetylcholine receptors in postsynaptic membranes and produce the defect in neuromuscular transmission in patients with myasthenia gravis by several methods: (1) complement-mediated membrane lysis;[29] (2) accelerated degradation of acetylcholine receptors;[3, 26, 29] (3) decreased incorporation (synthesis) of receptors;[33] (4) alterations in acetylcholine receptor–ion conductance interactions.[15] It is likely that each of these factors plays some role, of greater or lesser importance, in producing clinical myasthenia gravis.

Acetylcholine Receptor Antibodies and Clinical Myasthenia Gravis

In the preceding section, we have outlined several ways by which the autoimmune response in patients with myasthenia gravis could alter neuromuscular transmission and produce clinical weakness. It is clear that antibodies that bind to acetylcholine receptors are a significant factor in mediating the events that deplete acetylcholine receptors in the motor endplate. However, the exact relationship of acetylcholine receptor antibodies to the degree of clinical disease in myasthenia gravis is not known. Three questions remain: (1) Is the presence of acetylcholine receptor antibodies in a patient's serum sufficient to cause myasthenia gravis? (2) Are acetylcholine receptor antibodies the sole factor that determine the clinical course of myasthenia gravis? (3) Are all acetylcholine receptor antibodies the same?

We have carried out several studies that strongly suggest that the presence of acetylcholine receptor antibodies in a patient's serum is not always sufficient to cause clinical weakness, and that acetylcholine receptor antibodies are not the sole factor determining the clinical

state of patients with myasthenia gravis in at least some cases. There is also evidence that acetylcholine receptor antibodies are directed toward a number of determinants on the acetylcholine receptor.

There is no good correlation between absolute titer of acetylcholine receptor antibodies and the degree of clinical weakness present in patients with myasthenia gravis.[9, 32] Patients in remission from myasthenia may have a high antibody titer, while a patient in myasthenic crisis may have no detectable circulating acetylcholine receptor antibody (Table 3). However, it could be that not all acetylcholine receptor antibodies are the same. Some patients with myasthenia gravis may have acetylcholine receptor antibodies that bind strongly to the neuromuscular junction and are active in mediating events that deplete acetylcholine receptors. Other patients may have antibodies that do not mediate depletion of acetylcholine receptors. A similar explanation would account for the lack of correlation of antibody titer and clinical

Table 3. *Lack of Correlation of Serially Determined Acetylcholine Receptor Antibody Titer and Clinical State of Four Selected Patients with Myasthenia Gravis*

1. 18 year old woman				
Clinical State:	III, prethymectomy	III, 1 day post-thymectomy	3 mo. post-thymectomy; mild bulbar signs; no medication	
AB Titer:	N.S.	N.S.	N.S.	
2. 42 year old woman				
Clinical State:	III, hyperthyroid 1 mo. prethymectomy	1 Day post-thymectomy; Start prednisone Q.O.D.	2 mo. post-thymectomy moderate improvement	6 mo. post-thymectomy; mild bulbar signs only; prednisone
AB Titer:	9.1	7.4	7.9	9.2
3. 38 year old man				
Clinical State:	IIA 1 day prethymectomy	1 day post-thymectomy	3 mo. post-thymectomy; mild ocular signs only; Mestinon	
AB Titer:	N.S.	N.S.	1.8	
4. 41 year old woman				
Clinical State:	17 yr. post-thymectomy; remission	18 yr. unchanged	19 yr. unchanged	
AB Titer:	8.1	8.2	8.8	

Determinations of titer ($\times 10^{-9}$ M/L) were performed in quadruplicate. Classification of myasthenia gravis after Osserman and Genkins.[35]

state within individual patients. It could be that individual patients produced different populations of acetylcholine receptor antibodies at different times and that the clinical conditions of these patients vary with the type of antibodies produced at any one time. If the degree of clinical myasthenia depends only on the particular population of antibodies that are present, then any two individuals with the same acetylcholine receptor antibodies should have the same degree of clinical myasthenia gravis. Otherwise, one would have to conclude that some other factor(s) influence the effects of acetylcholine receptor antibodies on the neuromuscular junction.

Neonatal myasthenia gravis provides a unique opportunity to study the passive transfer of acetylcholine receptor antibodies from one individual to another. A number of cases of neonatal myasthenia gravis have been described in which acetylcholine receptor antibodies were detected in the serum of affected infants. In these cases, improvement of myasthenia in the infant correlated with a declining titer of antibody.

We have recently evaluated a case of neonatal myasthenia gravis in which the mother was in complete clinical remission despite the presence of high titers of acetylcholine receptor antibodies.[19] Her infant, however, had significant myasthenia that persisted until the acetylcholine receptor antibody titer declined (Table 4). The antibodies in the infant that caused weakness were passively transferred from the mother; yet the mother demonstrated no weakness. Thus, identical acetylcholine receptor antibodies can have different pathogenic potential in different individuals, and factors unique to each individual may determine the clinical course of myasthenia gravis. We do not know what these factors are, but immune factors, motor endplate sensitivity to antibody attack, hormones, or other factors may determine whether weakness will be present in some patients with myasthenia gravis.

While these experiments suggest that the clinical state of patients with myasthenia gravis may be modified by factors other than acetylcholine receptor antibodies, there is also evidence that the type of

Table 4. *Acetylcholine Receptor Antibody Titers of an Infant with Neonatal Myasthenia Gravis, and His Mother, Followed Longitudinally*

AGE	SEX	DELIVERY	1 MONTH	2 MONTHS
26	F	IIA		
Clinical State:		In remission last 6 mo. of pregnancy		Unchanged
AB Titer:		12.3		10.5
Infant	M			
Clinical State:		Moderate neonatal myasthenia gravis	Improved	Normal
AB Titer:		4.4	0.5	0

Titers ($\times 10^{-9}$ M/L) were performed in duplicate.

acetylcholine receptor antibodies is important in determining the clinical state of myasthenia gravis. There are several experiments that demonstrate that myasthenia gravis patients' immunoglobulins bind to different determinants on acetylcholine receptors. The original descriptions of acetylcholine receptor antibodies in patients with myasthenia gravis noted that: (1) these antibodies preferentially bound to rat extrajunctional receptors rather than junctional receptors, and (2) some patients' acetylcholine receptor antibodies blocked the binding of alpha-bungarotoxin while antibodies from other patients would bind to acetylcholine receptors without blocking alpha-bungarotoxin binding.[6, 7] It has recently been shown that patients' acetylcholine receptor antibodies have several binding specificities in regard to rat junctional and extrajunctional acetylcholine receptors.[43] The antibodies from different patients may bind to both junctional and extrajunctional receptors or bind to extrajunctional receptors alone; but they do not bind to junctional receptors alone. These experiments suggest that there are antigenic differences between rat junctional and extrajunctional acetylcholine receptors and also that different patients have different types of acetylcholine receptor antibody. Experiments noting that some myasthenia gravis immunoglobulins block the binding of acetylcholine receptors to conconavalin A demonstrate a third binding specificity for human acetylcholine receptor antibodies.[34]

The experimental animal model of myasthenia gravis provides direct evidence that antibodies directed against different sites on the acetylcholine receptor molecule can produce clinical weakness. The acetylcholine receptor of *Torpedo californica* consists of four polypeptides, molecular weights 38,000, 49,500, 57,000, and 64,000. Animals immunized with each of these purified subunits develop weakness. The animals immunized with the 38,000 dalton subunit, which apparently contains the acetylcholine binding site, develop more severe disease than animals immunized with other subunits. However, animals immunized with native acetylcholine receptor are more severely affected than those immunized with subunits of acetylcholine receptor.[30] This study demonstrates two principles: (1) Antibodies directed toward a number of sites on the acetylcholine receptor can cause weakness; (2) Severity of disease can be a function of the type of acetylcholine receptor antibodies produced.

In summary, there is evidence to substantiate the importance of acetylcholine receptor antibodies in clinical myasthenia gravis, but it also suggested that host factors can modify the response of the individual to the antibody:

1. Patients may have high titers of circulating acetylcholine receptor antibody, yet be clinically normal, or they may be severely ill and have no detectable antibody titer.

2. Identical acetylcholine receptor antibodies can produce different degrees of clinical weakness in different individuals.

3. Acetylcholine receptor antibodies are not directed against the same antigenic determinants on the acetylcholine receptor in all patients with myasthenia gravis.

4. Acetylcholine receptor antibody binding specificity can be a factor in determining the clinical state of patients with myasthenia gravis.

Why Does the Autoimmune Response Occur?

The cause of the immune attack on self antigens in myasthenia gravis is unknown. However, there are data concerning myasthenia gravis that do provide some clues about the origin of autoimmune diseases. Genetic factors and environmental factors both may be important in determining the occurrence of an autoimmune response.

One of the original observations that suggested that myasthenia gravis was an autoimmune disease was the frequent occurrence of other diseases of presumed autoimmune origin in patients with myasthenia gravis.[39] Certain individuals may have a predisposition to loss of self tolerance, possibly on a genetic basis. The delineation of autoimmune factors in Grave's disease strongly underlines this point.[5] Possibly more than 5 per cent of patients with myasthenia gravis have associated endocrine disease[36] in which autoimmunity plays an important role. It is possible that patients with myasthenia gravis have the predisposition to produce autoantibodies directed against a number of apparently unrelated proteins. This notion is also supported by the presence of antibodies to muscle contractile proteins in more than 30 per cent of patients with myasthenia gravis.[41] An increased frequency of HLA8 in young females with myasthenia gravis and HLA2 in older males with myasthenia gravis[24] is further evidence that genetic factors are important in determining the susceptability to loss of self tolerance.

There is evidence that environmental factors can determine the spectrum of autoantibodies produced, given the predisposition to loss of self-tolerance. Penicillamine is often used to treat the autoimmune disease, rheumatoid arthritis. Some of these patients develop myasthenia gravis with measurable titers of acetylcholine receptor antibodies during treatment.[38] Both weakness and acetylcholine receptor antibodies may decrease when penicillamine is withdrawn. Therefore, alteration of the cellular metabolic environment with a drug, penicillamine, induces antibody production in cells in which the potential for expressing this immune abnormality existed. Removal of this environmental stress eliminates the autoimmune attack on acetylcholine receptors.

The Role of the Thymus

The frequent involvement of the thymus in patients with myasthenia gravis remains an intriguing puzzle. More than 85 per cent of patients have abnormalities of the thymus. Fifteen percent of patients have thymomas and more than 70 per cent have an histologic abnormality that is referred to as thymic hyperplasia.[14] The hyperplastic thymus has an increased number of germinal centers resembling a failure of the thymus to undergo normal involution with age. It has been noted that these germinal centers contain an abnormal number of B-cells.[1]

Thymectomy increases the rate of remission among patients with myasthenia gravis and results in clinical improvement in most patients who undergo thymectomy.[25] This presents the question as to whether the thymic abnormality is the primary abnormality in patients with myasthenia gravis. A recent report that over 90 per cent of myasthenia gravis patients have circulating antibodies that bind to thymus cells may be relevant to this question.[27] If the thymus does have a role in maintaining self tolerance, then factors that alter this function could permit a loss of self-tolerance for any number of self antigens.

Since the removal of the thymus can induce remission from myasthenia gravis, it would seem likely that thymectomy removes a "negative factor" that causes loss of self tolerance. Cells capable of producing antibodies against self-antigens are normally present in the body, but these cells do not produce significant quantities of antibody under normal circumstances. The network theory of immune function[38] suggests that there are factors produced (possibly in the thymus) that can either suppress or activate antibody production. A suppressor cell can suppress the response of other immune cells which can also have suppressor or activator function. From the multitude of permutations available from this interconnected network, the abnormality in the thymus may result in the interruption of the normal interaction of suppressors and activators, the end result being production of antibodies directed against self antigens. In myasthenia gravis, antibodies are then produced against nicotinic acetylcholine receptors and other self antigens.

Therapeutic Implications

The localization of the neuromuscular transmission defect to a deficiency in acetylcholine receptors and the apparent autoimmune etiology of this defect have provided a theoretical rationale for judging past therapeutic approaches to myasthenia gravis. The traditional mainstay in the treatment of patients with myasthenia gravis has been oral anticholinesterases. The efficacy of these drugs can now be ascribed to maintaining the local concentrations of acetylcholine at the motor endplate and increasing the probability of acetylcholine binding to an acetylcholine receptor. However, it has long been recognized that not all patients are benefited by anticholinesterase therapy, and that sensitivity to these drugs may decrease in chronic treatment. The lack of effect of anticholinesterase medication in the acute situation may be explained: (1) by the total absence of postsynaptic acetylcholine receptors such that the increased acetylcholine concentration has nothing to act on, or (2) by the dramatic alteration of the geometry of the neuromuscular junction such that the widened intersynaptic cleft permits the increased acetylcholine to diffuse before it can act on the available acetylcholine receptors.

It has been demonstrated that chronic treatment of normal rats with high dose anticholinesterase can result in decreased concentrations of acetylcholine receptors at the motor endplate.[23] Such an effect could potentially increase the deficiency already present in myasthenia gravis and produce clinical deterioration and drug insensitivity. Thus,

the very medication used to treat patients with myasthenia gravis could, over a prolonged period, lower the concentration of acetylcholine receptors as effectively as could the acetylcholine receptor antibody. The beneficial effect of bringing patients into the hospital, safeguarding their respiratory function, and stopping anticholinesterase medication may be explained by a possible restoration of functional acetylcholine receptors. These patients would then be expected to reacquire sensitivity to anticholinesterase medication and such is the case.

The therapeutic effects of steroids and thymectomy are also further elucidated by the view of myasthenia gravis as an autoimmune disease. However, a complete explanation of why these therapies are useful is far from clear. It is likely that both thymectomy and steroids alter the immune response against the acetylcholine receptors and thereby benefit neuromuscular function. However, shortly after thymectomy or the institution of steroids, patients may improve clinically and yet acetylcholine receptor antibody titers may not change for several weeks or months. Thus, these therapeutic interventions are as likely to influence the host factors referred to above as they are to influence the antibody titers. Furthermore, these therapies may somehow repair the widened intersynaptic cleft and affect the geometry of the neuromuscular junction as much as they affect the immune attack on acetylcholine receptors.

Plasmaphoresis

The discovery that circulating antibodies against acetylcholine receptors are involved in the pathogenesis of myasthenia gravis has provided the rationale for new therapeutic approaches. Plasmaphoresis is in current use in patients who do not benefit from standard therapies.[16] Dau et al. have demonstrated that plasmaphoresis combined with immunosuppressive therapy can produce striking clinical improvement in treatment resistent patients. In these clinical trials, continuous flow plasma exchange was carried out until the patients total plasma volume was replaced. Serial exchanges were performed over extended periods of time. Acetylcholine receptor antibody titers were reduced to less than 25 per cent of original titers on the average. However, clinical improvement did not always correlate exactly with decreasing antibody titer. Although clinical improvement may be related to decreases of acetylcholine receptor antibody, it also may be related to the removal of immune activating factors or the addition of immune suppressing factors such as anti-idiotype antibody present in the normal replacement plasma.

Experimentation is currently being carried out with experimental animal myasthenia gravis to attempt to develop the technology to suppress the autoimmune response that causes myasthenia gravis. Bartfeld and Fuchs[12] have demonstrated that specific immunosuppression of experimental animal myasthenia gravis can be produced by immunization of animals with denatured acetylcholine receptor. Rabbits immunized with carboxymethylated acetylcholine receptors produced

antibodies that bound to acetylcholine receptor but did not cause weakness. Subsequent immunization with native receptors did not induce experimental autoimmune myasthenia gravis. In addition, animals with myasthenia gravis induced by immunization with native acetylcholine receptor showed clinical improvement when they were secondarily immunized with denatured acetylcholine receptor. The mechanism of this protective effect is not fully understood, but such findings hold out the hope that specific immunosuppression could be of benefit to human patients with myasthenia gravis.

CONCLUSIONS

Recent studies have established that myasthenia gravis is an autoimmune disease in which an immune attack directed against nicotinic acetylcholine receptors produces a defect in neuromuscular transmission. Humoral antibodies clearly play an important role in producing the neuromuscular transmission defect. Such antibodies may reduce the number of acetylcholine receptors as well as cause a widening of the synaptic cleft.

The disease may be initiated in a genetically susceptible individual by an alteration of thymic cell function which permits the production of antibodies to the acetylcholine receptor. These antibodies then initiate a series of reactions which ultimately decrease acetylcholine receptor density and alter the geometry of the neuromuscular junction. The altered acetylcholine receptor density and junctional morphology would be brought about both by complement-dependent extrusion of muscle membrane fragments into the cleft between nerve and muscle and by complement-independent accelerated degradation and decreased synthesis of the acetylcholine receptor. The extent of clinical deficit would be determined by the specificity and titer of the acetylcholine receptor antibodies as well as by host factors which modulate the metabolic response of the neuromuscular junction to the binding of antibody.

It is also likely that some patients have diseases that are clinically similar to myasthenia gravis but do not require the presence of antibody. Such cases are likely due to primary alterations in neuromuscular junction metabolism. Such a case has been described in which decreased amounts of acetylcholinesterase resulted in altered synaptic morphology and function.[20]

The successful marriage of basic research and clinical medicine that has resulted in our current understanding of the pathogenesis and therapy of myasthenia gravis is likely to continue to yield dividends as we focus efforts on the genetic and environmental factors which initiate the autoimmune response, the immune factors which regulate acetylcholine receptor antibody production, and the metabolic factors which regulate the synthesis and degradation of the acetylcholine receptor.

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REFERENCES

1. Abdou, N. I., Lisak, R. P., Zweiman, B., et al.: The thymus in myasthenia gravis: evidence for altered cell populations. New Eng. J. Med., *291*:1271–1275, 1974.
2. Abramsky, O., Aharonov, A., Webb, C., et al.: Cellular immune response to acetylcholine receptors — rich fractions in patients with myasthenia gravis. Clin. Exper. Immunol., *19*:11–16, 1975.
3. Albuquerque, E. X., Mayer, R. F., Appel, S. H., et al.: Effects of normal and myasthenic serum factors on innervated and chronically denervated mammalian muscles. Ann. N.Y. Acad. Sc., *274*:475–492, 1976.
4. Albuquerque, E. X., Rash, J. E., Mayer, R. F., et al.: An electrophysiological and morphological study on the neuromuscular junctions in patients with myasthenia gravis. Exper. Neurol., *51*:536–563, 1976.
5. Allison, A. C.: Self-tolerance and autoimmunity in the thyroid. New Eng. J. Med., *295*:821–827, 1976.
6. Almon, R. R., Andrew, C. B., and Appel, S. H.: Serum globulin in myasthenia gravis: inhibition of α-bungarotoxin binding to acetylcholine receptors. Science, *186*:55–57, 1974.
7. Almon, R. R., and Appel, S. H. Interaction of myasthenic serum globulin with the acetylcholine receptor. Biochem. Biophys. Acta, *393*:66–67, 1975.
8. Anwyl, R., Appel, S. H., and Narahashi, T.: Myasthenia gravis serum reduces acetylcholine sensitivity in cultured rat myotubes. Nature, 267:262–263, 1977.
9. Appel, S. H., Almon, R. R., and Levy, N.: Acetylcholine receptor antibodies in myasthenia gravis. New Eng. J. Med. *293*:760–761, 1975.
10. Appel, S. H., Anwyl, R., McAdams, M. W., et al.: Accelerated degradation of cultured rat myotube acetylcholine receptor with myasthenia gravis sera and globulins. Proc. Natl. Acad. Sci., *74*:2130–2134, 1977.
11. Appel, S. H., Elias, S. B., Chauvin, P., et al.: The role of acetylcholine receptor antibodies in myasthenia gravis. Fed. Proc. (in press).
12. Bartfeld, D., and Fuchs, S.: Specific immunosuppression of experimental autoimmune myasthenia gravis by denatured acetylcholine receptor. Proc. Natl. Acad. Sci., *75*:4006–4010, 1978.
13. Bender, A. N., Ringel, S. P., Engel, W. K., et al.: Myasthenia gravis: a serum factor blocking acetylcholine receptor of the human neuromuscular junction. Lancet, *1*:607–608, 1975.
14. Castleman, B.: The pathology of the thymus gland in myasthenia gravis. Ann. N.Y. Acad. Sci., *135*:496–503, 1966.
15. Cull-Candy, S. G., Miledi, R., and Trautman, A.: Acetylcholine-induced channels and transmitter release at human end plates. Nature, *271*:74–75, 197
16. Dau, P. S., Lindstrom, J. M., Cassel, C. K., et al.: Plasmaphoresis and immunosuppressive drug therapy in myasthenia gravis. New Engl. J. Med., 297:1134–1140, 1977.
17. Deverotes, P. N., and Fambrough, D. M.: Acetylcholine receptor turnover in membranes of developing muscle fibers. J. Cell Biol., *65*:335–358, 1975.
18. Elias, S. B., and Appel, S. H.: Acetylcholine receptor in myasthenia gravis: increased affinity for α-bungarotoxin. Ann. Neurol., *4*:250–252, 1978.
19. Elias, S. B., Butler, I., and Appel, S. H.: Neonatal myasthenia gravis in the infant of a myasthenic mother in remission. Ann. Neurol. (in press).
20. Engel, A. G., Lambert, E. H., and Gomez, M. R.: A new myasthenic syndrome with end-plate acetylcholinesterase deficiency, small nerve terminals, and reduced acetylcholine release. Ann. Neurol., *1*:315–330, 1977.
21. Engel, A. G., Lambert, E. A., and Howard, F. M.: Immune complexes (IgG and C_3) at the motor endplate in myasthenia gravis. Mayo Clin. Proc., 52:267–280, 1977.
22. Engel, A. G., and Santa, T.: Histometric analysis of the ultrastructure of the neuromuscular junction in myasthenia gravis and in the myasthenic syndrome. Ann. N.Y. Acad. Sci., *183*:35–58, 1971.
23. Fambrough, D. M., Drachman, D. B., and Satrjamurti, S.: Neuromuscular junction in myasthenia gravis: decreased acetylcholine receptors. Science, *182*:293–295, 1973.
24. Feltkemp, T. E. W., vandenBerg-Loonen, P. M., Nijenhuis, C. E., et al.: Myasthenia gravis, autoantibodies, and HEA antigens. Brit. Med. J., *1*:131–133, 1974.

25. Genkins, G., Papotestar, A. E., Horowitz, S. H., et al.: Studies in myasthenia gravis: early thymectomy. Electrophysiological and pathologic correlations. Amer. J. Med., 58:517–524, 1975.
26. Heinemann, S., Merlie, J., and Lindstrom, J. Modulation of acetylcholine receptor in rat diaphragm by anti-acetyl-choline receptor sera. Nature, 274:65–67, 1978.
27. Huang, S-H., Rose, J. W., and Mayer, R. F.: Assessment of cellular and humoral immunity of myasthenics. J. Neurol. Neurosurg. Psychiatry, *41*:394–403, 1978.
28. Jerne, N. K.: The immune system. Sci. Amer., 229:52–69, 1973.
29. Kao, I., and Drachman, D. B.: Myasthenic immunoglobulin accelerates acetylcholine receptor degradation. Science, *196*:527–529, 1977.
30. Lindstrom, J., Einarson, B., and Merlie, J. Immunization of rats with polypeptide chains from torpedo acetylcholine receptor causes an auto-immune response to receptors in rat muscle. Proc. Natl. Acad. Sci., *95*:769–773, 1978.
31. Lindstrom, J., and Lambert, E.: Content of acetylcholine receptor and antibodies bound to acetylcholine receptor in myasthenia gravis, experimental auto-immune myasthenia gravis and Eaton-Lambert Syndrome. Neurology, *28*:130–138, 1978.
32. Lindstrom, J. M., Seybold, M. F., Lennon, V. A., et al.: Antibody to acetylcholine receptor in myasthenia gravis: prevalence, clinical correlates, and diagnostic value. Neurology, 26:1054–1059, 1976.
33. Merlie, J., Changeux, J. P., and Gros, F.: Acetylcholine receptor degradation measured by pulselhase labeling. Nature, 264:74–76, 1976.
34. Mitty, T., Kornfeld, P., Tormay, H., et al.: Detection of anti-acetylcholine receptor antibodies in myasthenia gravis. New Eng. J. Med., 293:760–761, 1975.
35. Osserman, K. E., and Genkins, G. Studies in myasthenia gravis: review of twenty years experience in over 1200 cases. Mt. Sinai J. Med., *38*:497–537, 1971.
36. Osserman, K. E., Tsairis, P., and Weiner, L. B.: Myasthenia gravis and thyroid disease. J. Mt. Sinai Hosp., *34*:469–83, 1967.
37. Patten, B. M.: Myasthenia gravis: review of diagnosis and management. Muscle & Nerve, *1*:190–205, 1978.
38. Russell, A. S., and Lindstrom, J. M.: Penicillamine-induced myasthenia gravis associated with antibodies to acetylcholine receptor. Neurology, 28:847–849, 1978.
39. Simpson, J. A.: Myasthenia gravis: a new hypothesis. Scott. Med. J., 5:419–436, 1960.
40. Stanley, E. F., and Drachman, D. B.: Effect of myasthenic immunoglobulin on acetylcholine receptors of intact mammalian neuromuscular junctions. Science, *200*:1285–1287, 1978.
41. Strauss, A. J. L., Seegal, B. C., Hou, K. C., et al.: Immunofluorescence demonstration of a muscle binding complement-fixing serum globulin fraction in myasthenia gravis. Proc. Soc. Exp. Biol. Med., *105*:184–191, 1960.
42. Tokya, K. V., Drachman, D. B., Pestronk, A., et al.: Myasthenia gravis: passive transfer from man to mouse. Science, *190*:397–399, 1975.
43. Weinberg, C. B., and Hall, Z. W. Antibodies from patients with myasthenia gravis recognize determinants unique to extrajunctional acetylcholine receptors. Proc. Natl. Acad. Sci., 76:504–508, 1979.

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Metabolic Myopathies

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The muscle diseases in which a biochemical defect is known or postulated are commonly referred to as metabolic myopathies. This review deals with those genetic metabolic myopathies in which specific enzyme defects have been identified. Even though their number has steadily increased since McArdle's description of a myopathy due to impaired glycogen breakdown over 25 years ago, they still constitute a very small group of neuromuscular disorders in clinical practice. Their study, however, has greatly enhanced our current understanding of glycogen, lipid, and energy metabolism of human muscle.

DISORDERS OF GLYCOGEN METABOLISM

The glycogen storage diseases or glycogenoses are a group of uncommon disorders in which there is an inborn error of glycogen metabolism. The Cori classification contains eight enzymatically distinct forms (Table 1). Skeletal muscle is involved in five forms of glycogen storage disease. In three of these (Types II, V, and VII) muscle symptoms are the sole manifestation of the disease, while in the other two forms (Types III and IV) the clinical picture is complicated by liver dysfunction. Muscle is spared in the specific hepatic enzyme deficiencies (Types I, VI and VIII) of glycogen metabolism. These disorders fall beyond the scope of our review.

Disordered glycogen metabolism in skeletal muscle causes two basic clinical syndromes. One is characterized by exercise intolerance and myoglobinuria, as seen in myophosphorylase or phosphofructokinase deficiency, and the other by progressive muscle weakness.

Normal Glycogen Metabolism[82]

Glycogen is a polysaccharide composed of repeating units of glucose linked in chains by 1-4 bonds and branching through 1-6 link-

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Table 1. *Classification of Glycogen Storage Diseases*

TYPE	EPONYM	ENZYME DEFICIENCY	CLINICAL INVOLVEMENT OF MUSCLE
I	Van Gierke's disease	Glucose-6-phosphatase	No
II	Pompe's disease	Amylo-1,4-glucosidase (acid maltase)	Infantile form: Cardiomyopathy plus generalized weakness and hypotonia. Late onset form: Limb-girdle syndrome.
III	Cori-Forbes disease	Amylo-1,6-glucosidase (debrancher enzyme)	Adult onset proximal weakness, with or without distal wasting.
IV	Anderson's disease	Amylo-1,4→1,6-transglucosidase (brancher enzyme)	Rare, hypotonia, weakness
V	McArdle's disease	Muscle phosphorylase	Exercise intolerance, myoglobinuria.
VI	Hers' disease	Liver phosphorylase	No
VII	Tarui's disease	Phosphofructokinase	Exercise intolerance, myoglobinuria.
VIII	–	Liver phosphorylase b kinase	No

ages. Resting muscles utilize glucose and fatty acids for energy. Glycogen stores are utilized under the relatively hypoxic conditions present during strong rapid contractions. Synthesis and degradation of glycogen is controlled by separate enzyme systems (Fig. 1). The synthesis of glycogen starts with glucose-1-phosphate and consists of three steps: The enzyme UTP uridyltransferase attaches a uridyl-group from UTP to glucose-1-phosphate to form uridine-diphosphoglucose (UDPG). This nucleotide sugar is the substrate of the main synthetic enzyme glycogen synthetase, which attaches glucosyl units in an α-1,4 link to the growing polysaccharide chain. When the chains reach a certain length, another enzyme, amylo-1,4→1,6-trans-glucosidase or brancher enzyme transfers straight-chain glucosyl-units to another preformed chain by a 1-6 link to create a new branch. Glycogen synthetase exists in two forms — an active, independent, I-form, and a phosphorylated dependent or D-form, requiring the metabolite glucose-6-phosphate as cofactor. The rate of glycogen synthesis depends on the relative levels of the I- and D-forms of glycogen synthetase. The I-form is inversely proportional to the glycogen content of muscle, so that increased tissue levels of glycogen retard its biosynthesis.[24]

There are a number of glycogenolytic pathways. The most important pathway for the energy metabolism of the muscle cell is catalyzed by the action of two enzymes in sequence, phosphorylase and amylo-1,6-glucosidase or debrancher enzyme. Phosphorylase breaks 1-4 linkages from the peripheral chains of glycogen and releases single glucosyl-units as glucose-1-phosphate. This process stops four glucosyl-units short from the branch points, resulting in phosphorylase-limit-

dextrin (PLD). At this point the debrancher enzyme detaches the glucosyl units in the 1,6 position in a complex two-step reaction and thus sequentially allows phosphorylase to proceed with the complete degradation of glycogen. The released glucose-1-phosphate is converted to lactate or pyruvate via the Embden-Meyerhof glycolytic sequence. The principal degradative enzyme, phosphorylase, exists in two interconvertible forms. Phosphorylase b, the inactive form, is phosphorylated

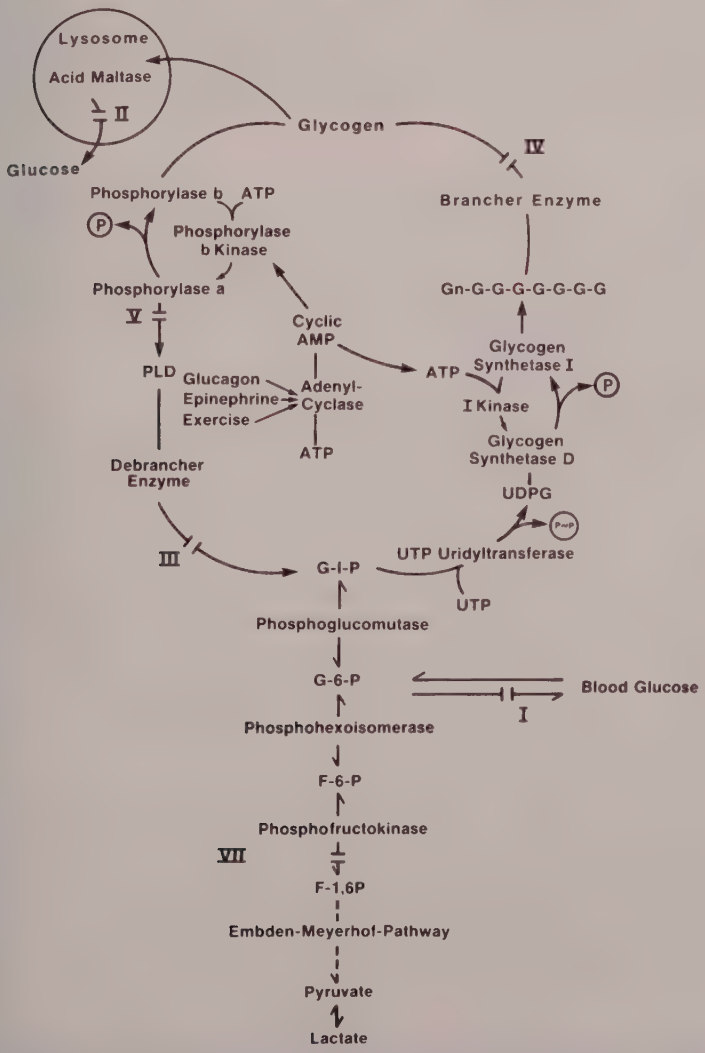

Figure 1. Synthesis and degradation of glycogen. Gn, glycogen polymer, G, glucosyl units. (Modified from Schimrig, K., et al.: Klin Wochenschr., 45:1–7, 1967.)

to its active form, phosphorylase a, under the influence of phosphorylase b kinase. This reaction is in turn activated by a protein kinase and requires epinephrine cyclic AMP and calcium ions released from the sarcoplasmic reticulum during excitation-contraction coupling. The same protein kinase, which activates phosphorylase b kinase also phosphorylates glycogen I synthetase to its inactive B form, thereby shutting off glycogen synthesis.

An alternative pathway of glycogenolysis occurs by the action of two amylo-1,4-glucosidases: acid and neutral maltase.[48] Acid maltase is a strictly lysosomal hydrolase, which can degrade glycogen to glucose directly at acid pH, and plays a role in the process of intracellular digestion of glycogen entrapped in autophagic vacuoles. The physiologic role of neutral maltase, which is bound in muscle to the sarcoplasmic reticulum, is obscure.

ACID MALTASE DEFICIENCY (GLYCOGENOSIS TYPE II)

Lysosomal acid maltase deficiency (AMD) produces two major clinical syndromes: A generalized, rapidly progressive, and fatal disease in infancy and a more benign neuromuscular disorder with onset in childhood or adult life.[37, 48]

Infantile Type (Pompe Disease)

The infantile type is characterized by glycogen accumulation in all tissues, particularly skeletal muscles, heart, and the central and peripheral nervous systems.[5, 16, 48, 50] Heart, skeletal muscle, and motor-neuron involvement lead to a stereotyped clinical picture: Symptoms begin a few months after birth and progress rapidly to death from cardiorespiratory failure within the first two years of life. The disorder manifests itself with muscle weakness, severe hypotonia, cardiomegaly with heart-failure, and in some cases with enlargement of the tongue and liver. The electrocardiogram shows a short PR interval, high voltage QRS complexes and signs of biventricular hypertrophy.[31, 51] Liver function is normal. The administration of epinephrine or glucagon is followed by a normal hyperglycemic response.

Late-Onset Acid Maltase Deficiency

Hers' discovery of the enzyme defect in infantile cases[46] has led to the recognition of individuals with milder cases surviving beyond infancy. Symptoms appear in childhood or adult life and, with few exceptions, are limited to skeletal muscle with no evidence of cardiac involvement. In the childhood type the disorder presents in early childhood with proximal limb and trunk muscle weakness.[37, 93, 95, 100] Progression and associated organomegaly are variable.[37] Death occurs usually before the end of the second decade from respiratory insufficiency, owing to severe involvement of respiratory muscles.[64]

In adult acid maltase deficiency, insidious limb-girdle weakness becomes manifest in the third or fourth decade.[29, 32, 33, 37, 53, 58] Muscles of the pelvic girdle are more involved than those of the shoulder girdle,

but considerable variation in the degree of wasting and weakness within an affected group of muscles has been observed. Craniobulbar muscles are spared except for rare tongue enlargement.[53] The course is usually slowly progressive. Involvement of respiratory muscles leads to severe pulmonary insufficiency in 25 to 50 per cent of the reported cases[37, 58] and may cause death.[29] The disorder is probably more common than the 14 reported cases would indicate, since many cases may go undiagnosed or unreported. Symptomatic heart and liver involvement have not been observed, although the enzyme defect has recently been documented in both organs.[29] Since the clinical features of adult acid maltase deficiency are not specific, it can be mistaken for other limb-girdle syndromes, notably limb-girdle dystrophy, polymyositis, or spinal muscular atrophy.

Laboratory Investigations

Serum creatine phosphokinase is consistently increased in all types of acid maltase deficiency. Liver function studies are normal. The administration of glucagon or epinephrine is followed by a normal hyperglycemic response and ischemic exercise induces a normal increase in lactic acid.[33] The electrocardiogram is, with very few exceptions,[29, 58] normal in late-onset cases. Electromyography characteristically shows abnormal resting activity consisting of fibrillation potentials, positive waves, bizarre high-frequency discharges similar to myotonic discharges in the absence of clinical myotonia, and short duration, polyphasic motor-unit potentials.[37] These abnormalities are widespread and of considerable diagnostic value in infantile cases,[50] but appear to a limited extent, with preferential trunk muscle involvement, in adult patients. These electromyographic changes are similar to the findings in polymyositis.

The muscle biopsy shows a vacuolar myopathy in all types of acid maltase deficiency. In infantile cases there is extensive vacuolation of muscle fibers of all skeletal muscles (Fig. 2) in contrast to adult cases in which the extent of involvement varies greatly from muscle to muscle, and could escape routine histologic observation when only a few fibers are affected.[37, 54] Paradoxically, histochemical type 1 fibers are more frequently vacuolated than type 2 fibers[18] although the latter normally contain more cytoplasmic glycogen. The majority of vacuoles contain periodic-acid-Schiff (PAS) positive granules which are removed after diastase digestion and show a very high activity of the lysosomal enzyme, acid phosphatase, suggesting lysosomal accumulation of glycogen.[37] These histochemical reactions are highly suggestive of acid maltase deficiency. On electron microscopy, glycogen accumulates freely in the sarcoplasm between myofilaments, in membrane bound sacs, and in autophagic vacuoles containing other cytoplasmic degradation products.[32, 33] (Fig. 3).

Biochemistry and Pathogenesis

The enzyme deficiency can be demonstrated by biochemical assay of muscle tissue[46, 68] or decreased urinary excretion of acid maltase.[67] Glycogen of normal structure is greatly increased in muscle tissue of

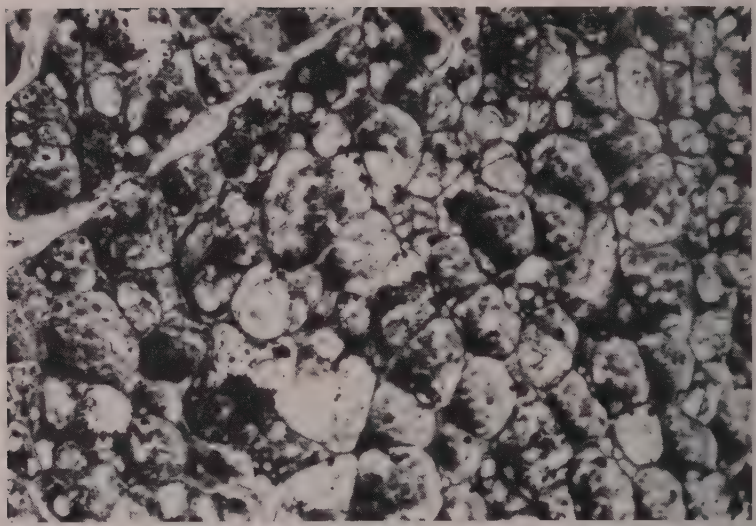

Figure 2. Acid maltase deficiency, infantile form. Light micrograph showing multiple vacuoles and accumulation of PAS-positive material at edges of muscle fibers. Transverse cryostat section, PAS ×375.

infantile cases, but to less and variable extent in children and adults.[33] The enzymes of the main glycogenolytic pathway show normal activity.[33]

In 1963 Hers[46] discovered the absence of acid maltase in tissues of patients with Pompe disease and formulated the concept of inborn lysosomal diseases. It has been proposed that in the process of the physiologic renewal of cells autophagy or self-digestion of small portions of the cytoplasm is a normal lysosomal function. In this process, glycogen is trapped with other cell components within a digestive vacuole or autolysosome. In type 2 glycogenosis, the absence of lysosomal acid maltase results in the accumulation of undigested glycogen within lysosomes.[47] This theory fails to explain the accumulation of free, cytoplasmic glycogen and why it is not metabolized by the cytoplasmic glycogenolytic pathway and the severe involvement of skeletal muscle, despite the generalized enzyme deficiency in all forms of acid maltase deficiency. A severe reduction of acid maltase activity has been demonstrated in muscle, liver,[33] heart, central nervous system,[29] and urine[67] in late-onset forms of the disorder, although there is little morphologic evidence of visceral glycogen storage in most cases of later onset.[29, 64] The enzyme deficiency and morphologic abnormalities have been recreated in muscle[4] and fibroblast-cultures.[1]

Another unresolved question relates to the biochemical basis for the clinical differences between infantile and late-onset forms. Angelini and Engel[2] found that neutral maltase, an enzyme associated with the sarcoplasmic reticulum, was decreased in muscle biopsies from infants, but not from patients with late-onset acid maltase deficiency.

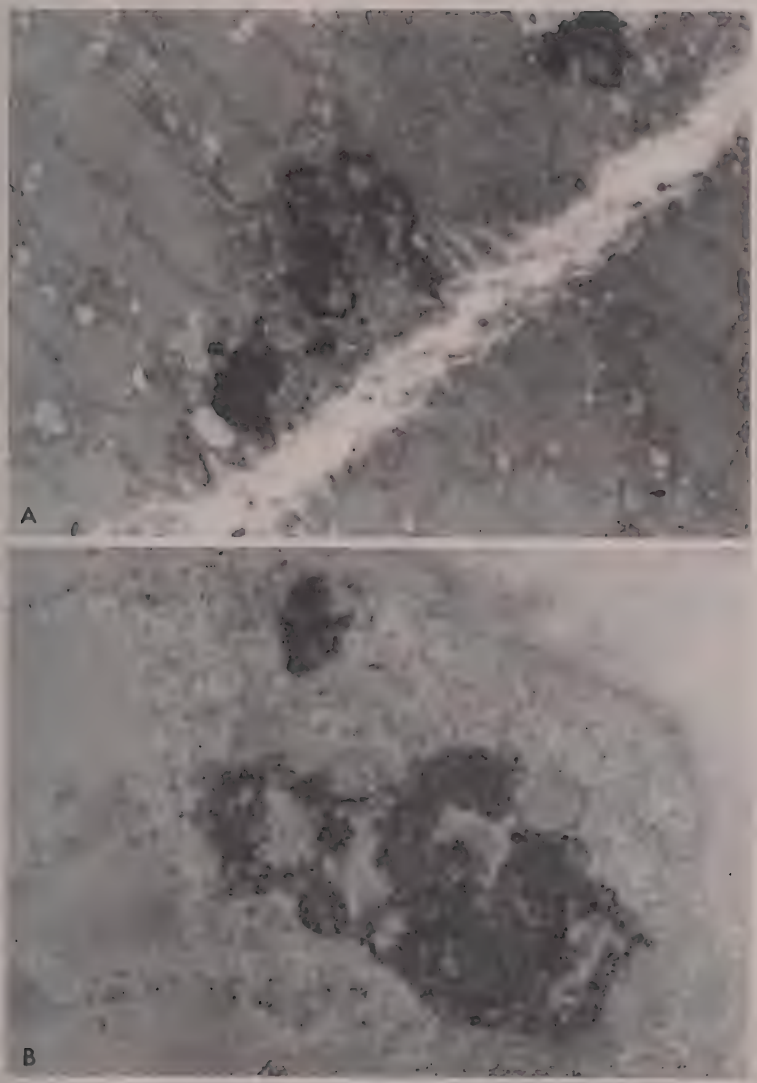

Figure 3. Electron micrographs of acid maltase deficiency, adult form. *A*, This longitudinal section contains four membrane bound glycogen deposits. Freely dispersed glycogen is accumulating in subsarcolemmal space. ×7300 *B*. Two lysosomes containing glycogen and lipid are present near the sarcolemma. ×13,700

They proposed that the normal activity of the neutral enzyme might partially compensate for the lack of acid maltase. However, using a sensitive fluorometric enzymatic assay, this observation was not confirmed by Mehler and DiMauro.[68] They found some residual acid maltase activity (3 to 12 per cent of normal) in muscle biopsies from patients with late-onset acid maltase deficiency but no activity in any tissue from infantile cases.

Both forms of acid maltase deficiency are transmitted as an autosomal recessive trait. Heterozygotes with partial enzyme deficiency have been identified.[34, 67] The prenatal diagnosis of infantile acid maltase deficiency is possible by amniocentesis performed in the 14th to 16th weeks of pregnancy, as acid maltase is lacking in cultured amniotic fluid cells.[72]

Therapy

Unsuccessful attempts to treat acid maltase deficiency include a ketogenic diet alone or in conjunction with epinephrine, lysosomal destabilizing agents, or administration of acid maltase derived from fungi.[26]

DEBRANCHER DEFICIENCY (GLYCOGENOSIS TYPE III)

In the absence of amylo-1,6-glucosidase, or debrancher enzyme, only the outer straight glucosyl-chains of glycogen can be broken down by phosphorylase. This results in an accumulation of glycogen with short outer chains (phosphorylase limit dextrin). This enzyme defect has been demonstrated in muscle, liver, leukocytes and erythrocytes.[99]

The clinical disorder is characterized by liver involvement in childhood. Hepatomegaly, growth retardation, fasting hypoglycemia and increased susceptibility to infection are the usual clinical manifestations. For reasons unknown, all symptoms and signs tend to disappear at puberty. Although the generalized enzyme defect involves muscle in most cases, clinical muscle involvement has been reported in only 10 patients.[15, 30, 71, 74, 75] Debrancher deficiency myopathy begins in adult life, long after the liver symptoms have disappeared, with slowly progressive weakness and distal wasting which is present in one-third of the cases.[15, 30] Atrophy of intrinsic hand muscles was a striking finding in the patient originally reported by Brunberg et al.[15] (Fig. 4). Exercise intolerance without cramps or myoglobinuria is surprisingly uncommon,[71, 75] although the metabolic block is only one step removed from that of myophosphorylase deficiency. Clinical and electrocardiographic signs of cardiac involvement are often present.[15, 30]

Laboratory Investigations

Administration of glucagon, which indirectly stimulates liver phosphorylase, or epinephrine which stimulates muscle and liver phosphorylase, produces no rise in blood glucose indicating deficient glycogen degradation. Venous lactate does not rise after ischemic forearm exercise.[15, 30] Serum creatine phosphokinase is markedly elevated.

Electromyographic studies show a mixed neuropathic and myopathic pattern with fibrillation potentials, pseudomyotonic discharges and short duration motor unit potentials.[15, 30] Muscle biopsy shows subsarcolemmal, coarse PAS positive vacuoles which are more abundant in type 2 fibers.[30] The vacuoles represent pools of glycogen particles in subsarcolemmal, or intermyofibrillar spaces.[15, 71]

Biochemistry

Increased glycogen with the structure of phosphorylase limit dextrin is found in muscle and erythrocytes.[30] Debranching of a phosphorylase-limit dextrin occurs by transfer of a maltotriosyl unit from a donor to an acceptor chain of the glycogen molecule, followed by hydrolysis of the α-1,6-glucosidic link. Van Hoof and Hers[99] described various sub-groups of glycogenosis type III with partial enzyme activity using different assays to analyze the sequential enzymatic reactions.

Inheritance is autosomal recessive. Osame et al.[74] described two siblings with debrancher deficiency myopathy. Therapy is limited to controlling hypoglycemia in childhood.

BRANCHER DEFICIENCY (GLYCOGENOSIS TYPE IV)

Brancher enzyme deficiency is characterized by the accumulation in liver, spleen and other organs, of an abnormal polysaccharide with long outer chains and few branching points, similar to amylopectin. The clinical picture of this rare glycogenosis is dominated by hepatosplenomegaly, progressive cirrhosis, and fatal hepatic failure in early

Figure 4. Debrancher deficiency myopathy. Severe atrophy of intrinsic hand muscles.

childhood.[41] Clinical involvement of muscle is overshadowed by severe debilitation owing to hepatic disease. Hypotonia, few spontaneous movements, contractures, wasting and decreased reflexes, have been reported in three cases.[41, 101] In one, heart and skeletal muscle contained granular deposits of basophilic material which reacted strongly with PAS and alcian blue stains.[88] Ultrastructurally, the deposits were composed of branched osmophilic filaments lying free in the intermyofibrillar and subsarcolemmal spaces, and were similar to those observed in liver and central nervous system.[88, 89]

Biochemistry

Brancher deficiency has never been demonstrated in muscle. During life the diagnosis can be made by the demonstration of the enzyme deficiency in leukocytes.[41] Transmission is autosomal recessive. No therapy is available.

MUSCLE PHOSPHORYLASE DEFICIENCY (GLYCOGENOSIS TYPE V, McARDLE DISEASE)

In 1951 McArdle[65] described a 30 year old patient with muscle cramps and stiffness after exercise and demonstrated a defect in anaerobic glycolysis. Subsequently, the enzyme defect was shown to be a deficiency of muscle phosphorylase.[76, 86] About 60 cases have been reported. Men outnumber women by a 4:1 ratio. The clinical picture is characterized by exercise intolerance.[76, 79] In early childhood, symptoms consist of easy fatigability and may escape recognition. After puberty, patients experience intermittent muscle pain, stiffness and weakness during vigorous exercise which resolves with rest. When the exercise limit is exceeded, painful "cramps" of the exercising muscles occur. In contrast to true muscle cramps, which are associated with rapid motor-unit firing, the shortened exercised muscle in McArdle disease is *electrically silent*, i.e., a true contracture.[60] Muscle necrosis with transient myoglobinuria may follow prolonged, severe exercise. Recurrent attacks of myoglobinuria are common, but acute renal failure as a consequence of myoglobinuria occurs rarely.[6, 43]

The degree of exercise intolerence may vary. In one patient, symptoms developed after isometric rather than isotonic exercise.[83] Improved performance after a "warm-up" period of nonstrenuous exercise has been termed "second wind phenomenon."[76] Increased mobilization of serum free fatty acids, providing muscle with an alternative source of energy and augmented blood flow to exercising muscles may be the basis of this clinical phenomenon.[77] Between attacks patients usually are normal, and can enjoy nearly normal lives if they avoid strenuous physical activity. As a late consequence of recurrent attacks of myoglobinuria, some patients develop a persistent proximal myopathy later in life.[86, 87] The clinical presentation of muscle phosphorylase deficiency can show considerable variation. Two adults presented with late-onset progressive muscle weakness instead of exercise-induced contractures.[40, 66] One infant had generalized hypo-

tonia and rapidly progressive weakness resulting in respiratory insufficiency and death at 13 weeks of age.[28]

Laboratory Investigations

A convenient screening test for myophosphorylase deficiency is the failure of lactic acid to rise after ischemic exercise (Fig. 5). The ischemic forearm exercise test is best performed under standard conditions:[70] The test is performed at rest and in a fasting state. Venous blood is collected without stasis by a catheter placed in a superficial cubital vein. After having obtained a resting, baseline blood sample, a cuff about the upper arm is inflated to a level above systolic pressure. The patient is then asked to grip an ergometer repetitively at about 60 strokes per minute sufficient to produce a work load of 4 to 7 kg per meter. The test was found to be reliable as long as work exceeded 4 kg per meter. Alternatively, the patient may compress a rolled sphygmomanometer cuff at a stroke rate of one per second. Adequate grip force is ensured by observing a rise in the mercury column of the sphygmomanometer. After an exercise period of one minute, the arm cuff is deflated and serial venous blood samples are collected at 1, 2, 3, 5, 10, and 20 minute intervals after the cessation of work. The peak lactate level occurs in normals at about 3 minutes and a 3 to 5-fold increase above the resting level should be seen. Reduced lactic acid production is not specific for McArdle disease; it can be seen in debrancher or phosphofructokinase deficiencies, and in other disorders in which a metabolic block of the glycolytic pathway is suspected.[84] It is also seen following the ingestion of ethanol in normals as well as alcoholics.[20] In McArdle disease, the ischemic forearm exercise causes a progressive

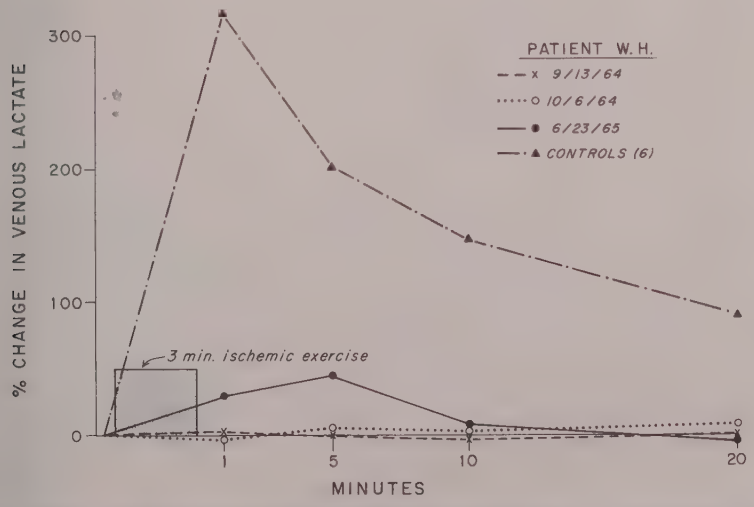

Figure 5. Venous lactate response to forearm ischemic exercise in a single patient with McArdle disease on three different occasions compared to the mean values of six age-matched normal controls.

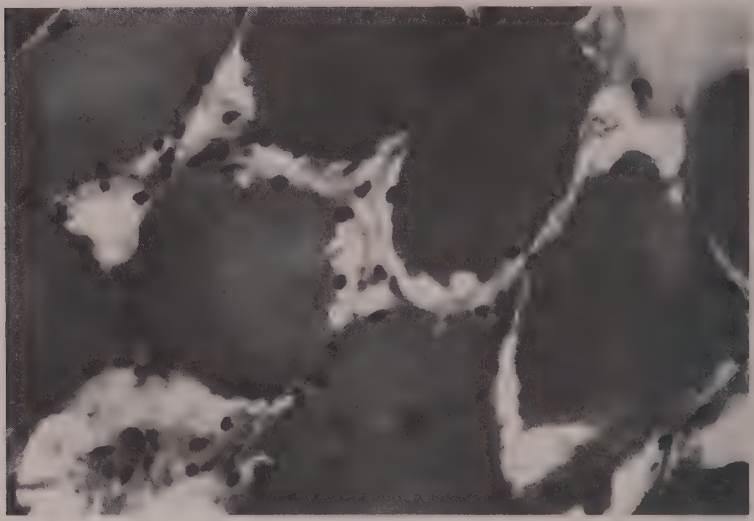

Figure 6. McArdle disease. Light micrograph showing prominent subsarcolemmal vacuoles. Transverse cryostat section. H. & E. ×550

electrically silent contracture of the flexor muscles.[81] Wrist and fingers remain locked in a tight grip and complete recovery may take one to several hours after circulation is restored. Serum creatine phosphokinase at rest is variably increased and myoglobin may be found in the urine. The muscle biopsy shows subsarcolemmal PAS-positive vacuoles and scattered necrotic or regenerating fibers (Fig. 6). The absence of phosphorylase activity can be demonstrated by enzyme histochemistry (Fig. 7). A positive staining reaction is seen only in blood vessel walls and regenerating fibers.[78] Ultrastructural studies reveal accumulation of glycogen under the sarcolemma and in intermyofibrillar spaces at the level of I bands.[90]

Biochemistry

In McArdle disease the defect in phosphorylase activity is *restricted to skeletal muscle*.[86] Other tissues have shown enzymatic activity, either by direct testing, or indirectly by the lack of clinical disorders of heart, liver and nervous system. It is of great interest that enzyme activity could be demonstrated histochemically in regenerating damaged muscle fibers[78] and muscle fibers in culture.[69] This reappearance of enzymatic activity in culture has been attributed to a fetal isoenzyme, which differs from mature muscle phosphorylase.[27] Muscle glycogen content is variably increased but may be normal.[40] The contractures are attributed to a depletion of ATP during vigorous exercise, when muscle depends primarily on glycogenolysis for energy. Depletion of ATP would retard the energy-dependent calcium ion uptake of the sarcoplasmic reticulum and thus impair relaxation. This postulated mechanism, however, could not be verified experimentally.[80]

McArdle disease shows genetic and biochemical heterogeneity. Most inherited cases demonstrate an autosomal recessive pattern, but two families with autosomal dominant transmission have been described.[19, 85] In addition, two different molecular types of McArdle disease have been recognized. In one no enzyme protein is detectable by immunological methods[79] while in the other an enzymatically inactive phosphorylase protein can be demonstrated immunologically.[6, 43] The clinical manifestations are identical, and phosphorylase is lacking in both by histochemical as well as biochemical methods.

The exercise tolerance of patients can be augmented by intravenous infusions of glucose and fructose, or by the hyperglycemic effect of glucagon.[76, 86] None of these measures, however is of therapeutic value for the long-term management of patients. Based on metabolic studies of the second wind phenomenon, the sublingual administration of isoproterenol, which increases plasma-free fatty acids and augments muscular blood flow, has been suggested.[77] Although occasional patients may be helped by sublingual isoproterenol, most find the adrenergic side-effects more troublesome than the disease.

MUSCLE PHOSPHOFRUCTOKINASE DEFICIENCY (GLYCOGENOSIS TYPE VII, TARUI DISEASE)

Phosphofructokinase (PFK) catalyzes the conversion of fructose-6-phosphate to fructose 1-6 diphosphate, a reaction which is a key step in the regulation of glycolysis. A defect of muscle phosphofructokinase

Figure 7. McArdle disease. Transverse cryostat section demonstrating complete absence of myophosphorylase activity. Blood vessel wall shows positive reaction. Myophosphorylase A reaction. × 300

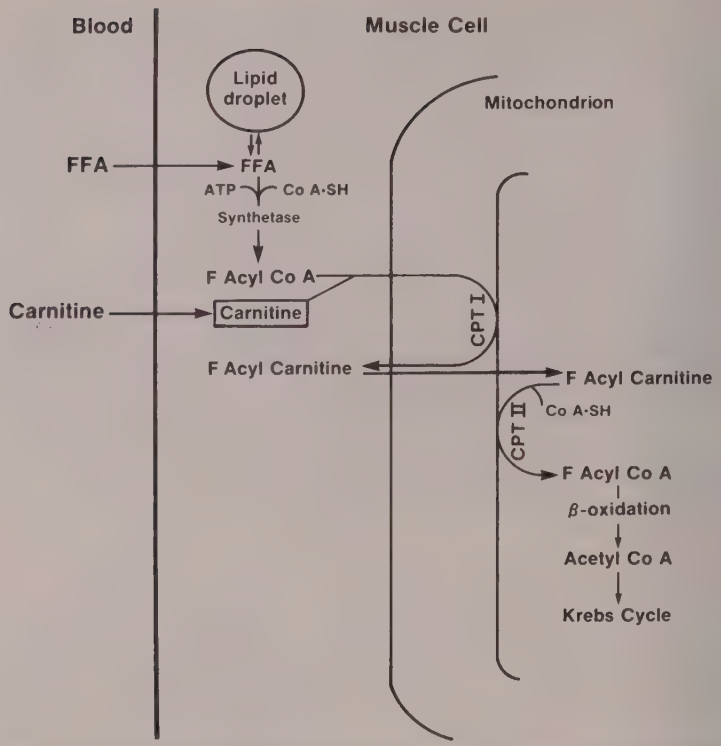

Figure 8. - Oxidation of long chain fatty acids in muscle. (Courtesy of Dr. S. DiMauro).

was first described in three siblings by Tarui and associates[96] and results in a clinical picture virtually identical to McArdle disease.[59, 97] Early in childhood patients experience exercise intolerance and muscle pain. Contractures followed by myoglobinuria may develop after strenuous work. The exercise-induced symptoms are frequently accompanied by nausea and vomiting, which is not common in McArdle disease.[59] One patient did not complain of exercise intolerance, but presented with progressive weakness in a scapulo-peroneal distribution.[92]

Laboratory Investigation

As in McArdle disease, there is no rise of venous lactate after ischemic forearm exercise. Serum creatine phosphokinase is moderately increased at rest. A mild hemolytic tendency is frequently associated with increased reticulocyte counts, raised serum bilirubin, and reduced erythrocyte life-span. This benign, subclinical erythrocyte abnormality may serve as a diagnostic clue and is the result of a partial defect of the red blood cell phosphofructokinase activity.[59, 96] Muscle pathology and degree of glycogen accumulation are similar to McArdle disease. The diagnosis is established by the direct measurement of

phosphofructokinase activity in a muscle biopsy by biochemical or histochemical methods. The histochemical reaction for phosphorylase is preserved, but the phosphofructokinase reaction is absent.[9]

Biochemistry

In affected patients, phosphofructokinase activity is virtually absent in muscle, reduced to half-normal in erythrocytes, and normal in leukocytes[59, 96] Immunological studies of one patient's muscle failed to detect an enzyme protein which cross-reacted with purified human muscle phosphofructokinase.[59] It is suggested that human muscle phosphofructokinase is composed of identical muscle-type (M) subunits, while the erythrocyte isoenzyme contains both muscle-type and red blood cell-type (R) subunits. Genetic lack of the M-subunit explains the partial defect of erythrocyte phosphofructokinase, the hemolytic tendency, and the absence of muscle phosphofructokinase activity.[61]

Inheritance of muscle phosphofructokinase deficiency appears to be autosomal recessive.[96] No therapeutic attempts which might increase the exercise tolerance in these patients, have been reported. Since the enzyme defect affects glycolysis, the metabolic block cannot be bypassed by administration of glucose or hyperglycemic agents. Dietary regimens or drugs which increase levels of plasma fatty acids might be beneficial.

DISORDERS OF LIPID METABOLISM

Both glycogen and lipids are important for the energy needs of muscle. Glycogenolysis plays the major role in providing energy for short duration, high intensity work, while free fatty acids are the major source of energy at rest, in the fasting state and during prolonged, low intensity exercise. The oxidation of fatty acids occurs in mitochondria, but long-chain fatty acids, i.e., palmitic and oleic acid, can cross the mitochondrial membrane only when combined with carnitine, which acts as a carrier. Carnitine is synthesized in the liver from the aminoacid lysine and is transported via the blood to muscle and other tissues. The much higher concentration of carnitine in muscle as compared to plasma implies that the uptake by muscle depends on an active transport mechanism.[38] A simplified scheme[26] of the long-chain fatty acid metabolism is outlined in Figure 8: Once free fatty acids have crossed the muscle cell membrane, they are activated by an ATP dependent reaction to fatty acyl-CoA. The long chain fatty acyl group is then attached to carnitine by carnitine palmityltransferase I (CPT I) located on the outer surface of the inner mitochondrial membrane. Fatty acylcarnitine can now cross the mitochondrial barrier. Once inside the mitochondrion, a second carnitine palmityltransferase (CPT II) catalyzes the reverse reaction with formation of fatty acyl-CoA. The fatty acyl-CoA then undergoes the intra-mitochondria process of beta-oxidation.

Two disorders of muscle lipid metabolism have recently been bio-

Table 2. *Disorders of Muscle Lipid Metabolism*

DEFECT	CLINICAL INVOLVEMENT OF MUSCLE	LIPID STORAGE IN MUSCLE
Carnitine Deficiency	a. Myopathic form: Progressive weakness, proximal > distal	Yes
	b. Systemic form: Progressive weakness, plus episodic hepatic insufficiency	Yes
Carnitine palmityltransferase Deficiency	Recurrent myoglobinuria provoked by prolonged exercise with or without fasting	Rare
?	Progressive weakness proximal > distal	Yes

chemically identified (Table 2). One, carnitine deficiency, originally reported by A. G. Engel and Angelini,[36] is characterized clinically by progressive weakness. The other carnitine palmityltransferase deficiency[25] is characterized by recurrent myoglobinuria. Carnitine deficiency leads to an intracellular accumulation of neutral lipids in myofibers and is thus, a lipid storage myopathy.[11, 35] Lipid storage myopathies with normal muscle carnitine levels have also been reported,[56] and the biochemical errors of these cases remain to be elucidated. In addition, an intracellular excess of lipid in myofibers is frequently present in many cases of the so-called mitochondrial myopathies which are characterized by ultrastructural mitochondrial abnormalities.[12] Excessive accumulation of lipid droplets in type 1 fibers was also reported in a patient with a functional mitochondrial defect, pyruvate decarboxylase deficiency, who had episodic ataxia, but no neuromuscular symptoms.[8] The overlap of mitochondrial and lipid storage myopathies is not surprising since lipid utilization is an intramitochondrial phenomenon.

CARNITINE PALMITYLTRANSFERASE DEFICIENCY

Since the original report of carnitine palmityltransferase deficiency presenting with recurrent myoglobinuria and transient renal failure in two brothers,[7, 25] 8 other cases have been reported.[14, 17, 22, 23, 45, 52, 62, 91] The clinical picture in these patients is characterized by recurrent episodes of myoglobinuria associated with muscular pain provoked by prolonged exercise — mountain hiking, long distance running, playing soccer — by fasting or, by a combination of the two. Muscle pains are present from childhood in most patients, but attacks of myoglobinuria are unusual before adolescence. Renal failure and transient weakness with painful muscle swelling may follow a severe attack of myoglobinuria.[7, 17, 23] Between attacks muscle strength is normal. The relative predominance of carbohydrates as an energy source in early exercise allows the patient with carnitine palmityltransferase deficiency to function normally unless the exercise is prolonged. In contrast to phos-

phorylase and phosphofructokinase deficiency, there is no intolerance to brief, strenuous exercise, no second wind phenomenon, and contracture cannot be induced by ischemic exercise.

Laboratory Investigations

A normal rise of venous lactate after ischemic exercise readily excludes a defect in anaerobic glycolysis. Serum creatine phosphokinase (CPK) is normal at rest but sharply elevated during episodes of myoglobinuria. Hypertriglyceridemia was found in three patients and has been related to impaired peripheral fatty acid utilization.[7, 23] The muscle biopsy is either normal, or may have a slight excess of intrafiber lipid droplets.[22, 52] Although the diagnosis rests ultimately on the biochemical assay of carnitine palmityltransferase activity in muscle, two screening tests may provide helpful diagnostic clues:[17] During exercise performed for 2 hours on a bicycle ergometer,[13] a patient with carnitine palmityltransferase deficiency showed a prolonged and inordinate increase in creatine phosphokinase. An even simpler provocative test is a 38 hour fast during which only non-caloric liquids are taken. In patients with carnitine palmityltransferase deficiency a sharp increase of serum creatine phosphokinase occurs.[7, 17, 52] Less consistently, there is a delayed or decreased formation of plasma and urinary ketones.[7, 17]

Biochemistry

Biochemical investigations of muscle tissue reveal that carnitine palmityltransferase activity is markedly decreased but carnitine, glycogen, phosphorylase, and phosphofructokinase are normal.[25] The enzyme defect is also found in white blood cells, cultured fibroblasts, and liver.[23, 26] Liver involvement results in impaired long-chain fatty acid oxidation and decreased ketone body production during fasting.

Despite male predominance, inheritance is autosomal recessive. Intermediate values of carnitine palmityltransferase activity were found in white blood cells from the asymptomatic, presumably heterozygote mother of the first described pair of affected brothers.[26]

Therapy

Patients should be warned about the risks of prolonged physical activity and skipping meals. A low-fat, carbohydrate-rich diet has been found effective in reducing the frequency of myoglobinuric attacks.[52]

CARNITINE DEFICIENCY

Carnitine deficiency as a cause of lipid storage myopathy was first demonstrated by Engel and Angelini.[36] Since this report more than 10 cases have been identified and they seem to fall into two distinct groups. In the first group, carnitine deficiency is largely limited to muscle and presents with progressive weakness, while in the other a systemic defect of carnitine leads to both muscle and liver involvement.

Muscle Carnitine Deficiency

The clinical picture of muscle carnitine deficiency is dominated by a slowly progressive myopathy.[12, 38, 55, 63, 98] With the exception of a single case[63] most patients have become symptomatic in childhood. Weakness is of the limb-girdle type, but may also affect facial and pharyngeal muscles. A common symptom, even more so in systemic cases, is weakness of the neck with loss of proper head control.[12, 35, 57] Deep tendon reflexes are decreased to absent. Cardiac involvement was suggested by an abnormal electrocardiogram in one patient[98] and probably caused heart failure and death at 2 years of age in another.[44]

Laboratory Investigations

Serum creatine phosphokinase is moderately increased in most patients. Electromyography reveals a typical "myopathic" pattern with abundant polyphasic, small amplitude, short duration motor unit potentials. Denervation and reduction in motor nerve conduction velocity was seen in one patient, but the disorder was complicated by diabetes mellitus.[63] The muscle biopsy reveals excessive intrafiber lipid droplets, most abundant in the type 1 fibers, readily seen with the Oil Red O reaction. Ultrastructurally, the lipid droplets appear as empty vacuoles or contain low electron dense material. They lack limiting membranes and are often adjacent to mitochondria which may contain abnormal inclusions.[11, 35] Lipid vacuoles were also found in leukocytes[3, 63, 94] and the Schwann cells of peripheral nerve.[63] Other evidence of defective lipid metabolism is typically absent in the myopathic form of carnitine deficiency. Serum carnitine levels are normal or only slightly decreased, as are serum cholesterol and triglycerides. Unlike the findings in carnitine palmityltransferase deficiency, fasting results in normal ketone body production suggesting normal hepatic lipid catabolism.[38, 98]

Biochemistry

In vitro oxidation studies of muscle tissue demonstrated impaired oxidation of labeled long-chain fatty acids which could be corrected by the addition of carnitine.[36] Carnitine is markedly reduced in muscle to one-tenth to one-fifth of normal. Carnitine deficiency of muscle leads to defective transport of long chain fatty acids into mitochondria and subsequently to intracellular triglyceride storage. The etiology of muscle carnitine deficiency has not been established. Since serum carnitine is normal or only slightly decreased, a defect of the active carnitine transport mechanism from blood into muscle has been proposed.[38] In one patient, liver carnitine was studied and found to be normal.[38]

Autosomal recessive inheritance is probable. Genetic transmission was demonstrated in one family. Both asymptomatic parents of the affected propositus showed half-normal muscle carnitine levels.[98] The assay of muscle carnitine may thus be important in identifying the heterozygote.

Therapy

Patients have improved with prednisone.[35, 55, 98] In recent reports, oral administration of carnitine in combination with a medium chain triglyceride diet resulted in marked improvement of muscle strength,[3, 38, 57] although muscle carnitine levels remained low.[38, 57] More controlled experience is needed to evaluate the efficacy of replacement therapy as one patient improved spontaneously after a relapsing and remitting course.[12]

SYSTEMIC CARNITINE DEFICIENCY

In the generalized or systemic form, liver involvement accompanies the myopathy.[10, 21, 39, 57] These patients develop intermittent hepatic enlargement and insufficiency with concomitant encephalopathy and attacks of metabolic acidosis. With onset of muscle weakness in early childhood, the disease pursues a fluctuating but progressive course, ending with death before the age of 20.[21, 39]

Laboratory Investigations

Decreased levels of serum carnitine have been recorded in all patients studied.[21, 57] Liver function studies are abnormal during acute episodes of hepatic insufficiency. The repeatedly observed lactic acidosis may be a consequence of accelerated glycolysis and augmented oxidation of ketogenic amino acids as fatty acids cannot be utilized as energy source. Excessive extramitochondrial oxidation of long-chain fatty acids which is not carnitine dependent, may contribute to the acidosis.[39] In addition to muscle, intracellular lipid storage was found at autopsy in liver, heart and tubular epithelium of kidney.[10, 21]

Biochemistry

Carnitine content was decreased in muscle, liver and heart in all patients studied, either by biopsy[57] or in postmortem tissues.[21] The low carnitine concentration in both liver and serum suggests a defect of the hepatic synthesis of carnitine, although this lacks confirmation.[57] Improvement of strength with concomitant normalization of liver function and serum carnitine level was reported in one patient after carnitine replacement therapy, although liver and muscle carnitine remained unchanged.[57]

Despite recent advances in our understanding of lipid metabolism of muscle, many questions are still unresolved. The biochemical defects of lipid storage myopathies with normal carnitine content await further clarification. Furthermore, it is intriguing that the similar metabolic defect of carnitine palmityltransferase deficiency produces typically no lipid storage myopathy and a very different clinical syndrome.

MUSCLE ADENYLATE DEAMINASE DEFICIENCY

Recently, Fishbein and collaborators[42] reported deficient myoadenylate deaminase in five young men. They presented with weakness, muscle stiffness and aching after exercise. Serum creatine phosphokinase was elevated in three. Electromyographic studies showed occasional polyphasic motor unit potentials. Muscle biopsies were histologically normal but lacked adenylate deaminase by a histochemical staining method. Biochemical assay for adenylate deaminase confirmed the enzyme deficiency. The sarcoplasmic enzyme, adenylate deaminase, catalyzes the irreversible deamination of adenosine monophosphate (AMP) to inosine monophosphate and leads to the production of ammonia in muscle, which accompanies the rise of lactic acid during muscle contraction. Its function in muscle may be the removal of AMP to maintain a high ratio of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) during strenuous muscular activity. The production of ammonia can be measured by a standard ischemic forearm exercise test with serial, simultaneous venous lactate and ammonia determinations to estimate glycolytic and muscle adenylate deaminase activity. Failure of plasma ammonia to rise may be used as a clinical screening test. Sex-linked recessive transmission was documented in one family.[49] A young boy and his male maternal cousin presented with post-exercise muscle pain and minimal proximal pectoralis weakness. Muscle adenylate deaminase activity was absent in the symptomatic patient, normal in his father, and half-normal in the mother.

Muscle pain is one of the most common symptoms of neuromuscular disease. The causes of such pain are various but a large proportion of patients complaining of myalgia remain undiagnosed. Although it may be too early to draw firm conclusions from these few cases, myoadenylate deaminase deficiency holds the promise to be another recognizable genetic disorder of deranged energy metabolism of muscle leading to exercise induced symptoms.

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REFERENCES

1. Angelini, C., Engle, A.G., and Titus, J.L.: Adult acid maltase deficiency. Abnormalities in fibroblasts cultured from patients. New Eng. J. Med., 287:948–951, 1972.
2. Angelini, C., and Engle, A.G.: Comparative study of acid maltase deficiency. Biochemical differences between infantile, childhood and adult types. Arch. Neurol., 26:344–349, 1972.
3. Angelini, C., Lücke, S., and Cantarutti, F.: Carnitine deficiency of skeletal muscle: Report of a treated case. Neurology (Minneap.) 26:633–637, 1976.

4. Askanas, V., Engle, W.K., DiMauro, S., et al.: Adult onset acid maltase deficiency. Morphologic and biochemical abnormalities reproduced in cultured muscle. New Eng. J. Med., 294:573–578, 1976.
5. Araoz, C., Sun, C.N., Shenefelt, R., et al.: Glycogenosis type II (Pompe's Disease): Ultrastructure of peripheral nerves. Neurology (Minneap.), 24:739–742, 1974.
6. Bank, W.J., DiMauro, S., and Rowland, L.P.: Renal failure in McArdle's disease. New Eng. J. Med., 287:1102, 1972.
7. Bank, W.J., DiMauro, S., Bonilla, E., et al.: Disorder of muscle lipid metabolism and myoglobinuria. Absence of carnitine palmityltransferase. New Eng. J. Med., 292:443–449, 1975.
8. Blass, J.P., Kark, P.A.R., and Engel, W.K.: Clinical studies of a patient with pyruvate decarboxylase deficiency. Arch. Neurol., 25:449–460, 1971.
9. Bonilla, E., and Schotland, D.L.: Histochemical diagnosis of muscle phosphofructokinase deficiency. Arch. Neurol., 2:8–12, 1970.
10. Boudin, G., Mikol, J., Guillard, et al.: Fatal systemic carnitine deficiency with lipid storage in skeletal muscle, heart, liver and kidney. J. Neurol. Sci., 30:313–325, 1976.
11. Bradley, W.G., Hudgson, P., Gardner-Medwin, D., et al.: Myopathy associated with abnormal lipid metabolism in skeletal muscle. Lancet, 1:495–498, 1969.
12. Bradley, W.G., Tomlinson, B.E., and Hardy, M.: Further studies of mitochondrial and lipid storage myopathies. J. Neurol. Sci., 35:201–210, 1978.
13. Brooke, M.H., Carroll, J.E., and Davis, J.E.: The prolonged exercise test in patients with muscle pains and fatigue. Ann. Neurol. 1:499, 1977.
14. Brownell, A.K.W., Severson, D.L., and Thompson, C.D.: Rhabdomyolysis secondary to carnitine palmityl transferase deficiency. IV International Congress on Neuromuscular Disease. Abstracts 205, 1978.
15. Brunberg, J.A., McCormick, W.F., and Schochet, S.S.: Type III Glycogenosis. An adult with diffuse weakness and muscle wasting. Arch. Neurol. 25:171–178, 1971.
16. Cardiff, D.F.: A histochemical and electronmicroscopic study of skeletal muscle in a case of Pompe's disease (Glycogenosis II). Pediatrics, 37:249–259, 1966.
17. Carroll, J.E., Brooke, M.H., Devivo, D.C., et al.: Biochemical and physiologic consequences of carnitine palmityl transferase deficiency. Muslce & Nerve, 1:103–110, 1978.
18. Chou, S.M., Gutman, L., Martin, J.D., et al.: Adult type acid maltase deficiency: Pathologic features. Neurology (Minneap.), 24:394, 1974.
19. Chui, L.A., and Munsat, T.L.: Dominant inheritance of McArdle syndrome Arch Neurol., 33:636–641, 1976.
20. Chui, L.A., Munsat, T.L., and Craig, J.R.: Effect of ethanol on lactic acid production by exercised normal muscle. Muscle & Nerve, 1:57–61, 1978.
21. Cornelio, F., DiDonato, S., Peluchetti, D., et al.: Fatal cases of lipid storage myopathy with carnitine deficiency. J. Neurol. Neurosurg. Psychiatry, 40:170–178, 1977.
22. Cumming, W.J.K., Hardy, M., Hudgson, P., et al.: Carnitinepalmityl-transferase deficiency. J. Neurol. Sci., 30:247–258, 1976.
23. DiDonato, S., Cornelio, R., Pacini, L., et al.: Muscle Carnitine Palmityltransferase Deficiency. A Case with Enzyme Deficiency in Cultured Fibroblasts. Ann. Neurol., 4:465–467, 1978.
24. DiMauro, S., Rowland, L.P., and DiMauro, P.M.: Control of glycogen metabolism in human muscle: Evidence from glycogen storage diseases. Arch. Neurol., 23:534–540, 1970.
25. DiMauro, S.M., and DiMauro, P.M.: Muscle carnitine palmityltransferase deficiency and myoglobinuria. Science. 182:929–931, 1973.
26. DiMauro, S. and Eastwood, A.B.: Disorders of Glycogen and Lipid Metabolism. Griggs, R.C., Moxley, III, R.T., eds.: Advances in Neurology, Vol. 17. New York, Raven Press, 1977, pp. 123–142.
27. DiMauro, S., Arnold, S., Miranda, A.T., et al.: McArdle disease: The mystery of reappearing phosphorylase activity in muscle culture. A fetal isoenzyme. Ann. Neurol, 3:60–66, 1978.
28. DiMauro, S., and Hartlage, P.L.: Fatal infantile form of muscle phosphorylase deficiency. Neurology, 28:1124–1129, 1978.
29. DiMauro, S., Stern, L.Z., Mehler, M., et al.: Adult-onset acid maltase deficiency: A post mortem study. Muscle & Nerve, 1:27–36, 1978.
30. DiMauro, S., Hartwig, G.B., Hays, A., et al.: Debrancher deficiency myopathy: A case of mistaken identity? IV International Congress on Neuromuscular diseases. 381 (Abstract) 1978.
31. DiSant, Agnese, P.A., Anderson, D.H., Mason, H.H., et al.: Glycogen storage disease of the heart. Report of two cases in siblings with chemical and pathologic studies. Pediatrics, 6:402–424, 1950.

32. Engel, A.G., and Dale, A.J.D.: Autophagic glycogenosis of late-onset with mitochondrial abnormalities: Light and electron microscopic observations. Mayo Clin. Proc., *43*:233–279, 1968.
33. Engle, A.G.: Acid maltase deficiency in adults. Studies in four cases of a syndrome which may mimic muscular dystrophy or other myopathies. Brain, *93*:599–616, 1970.
34. Engle, A.G., and Gomez, M.R.: Acid maltase levels in muscle in heterozygous acid maltase deficiency, and in non-weak and neuromuscular disease controls. J. Neurol. Neurosurg. Psychiatry, *33*:801–804, 1970.
35. Engel, A.G., and Siekert, G.: Lipid storage myopathy responsive to prednisone. Arch. Neurol., *27*:174–181, 1972.
36. Engel, A.G., and Angelini, C.: Carnitine deficiency of human skeletal muscle with associated lipid storage myopathy. A new syndrome. Science, *179*:899–901, 1973.
37. Engle, A.G., Gomez, M.R., Seybold, M.E., et al: The spectrum and diagnosis of acid maltase deficiency. Neurology, *23*:95–106, 1973.
38. Engle, A.G., Angelini, C., Nelson, R.A.: Identification of carnitine deficiency as a cause of human lipid storage myopathy. Milhorat, A.T., (ed.): Exploratory Concepts in Muscular Dystrophy. New York, Excerpta Medica, 1974, Vol. 2, pp. 601–618.
39. Engel, A.G., Banker, B.Q., and Eiben, R.M.: Carnitine deficiency: Clinical, morphological and biochemical observations in a fatal case. J. Neurol. Neurosurg. Psychiatry, *40*:313–322, 1977.
40. Engel, K.W., Eyerman, E.L., and Williams, H.E.: Late-onset type of skeletal muscle phosphorylase deficiency: A new familial variety with completely and partially affected subjects. New Eng. J. Med., *268*:135–137, 1963.
41. Fernandes, J., and Huijing, F.: Branching enzyme-deficiency glycogenosis: Studies in therapy. Arch. Dis. Child., *43*:347–352, 1968.
42. Fishbein, W.N.., Armbrustmacher, V.W., and Griffin, J.L.: Myoadenylate deaminase deficiency: A new disease of muscle. Science, *200*:545–548, 1978.
43. Grünfeld, J.P., Ganeval, D., Chanard, J., et al.: Acute renal failure in McArdle's disease: Report of two cases. New Engl. J. Med., *286*:1237–1241, 1972.
44. Hart, Z.H., Chang, C.H., DiMauro, S., et al.: Muscle carnitine deficiency and fatal cardiomyopathy. Neurology *28*:147–151, 1978.
45. Herman, J., and Nadler, H.L.: Recurrent myoglobinuria and muscle carnitine palmityltransferase deficiency. J. Pediatr., *91*:247–250, 1977.
46. Hers, H.G.: α-Glucosidase deficiency in generalised glycogen storage disease (Pompe's disease). Biochem. J., *68*:11–16, 1963.
47. Hers, H.G.: The concept of inborn lysosomal disease. *In* Hers, H.G., and Van Hoof, F., (eds.): Lysosomes and Storage Diseases. New York, Academic Press, 1973, pp. 147–171.
48. Hers, H.G., and deBarsy, T.: Type II glycogenosis (acid maltase deficiency). *In* Hers, H.G.Van Hoof, F., eds.: Lysosomes and Storage Diseases. New York, Academic Press, 1973, pp. 197–216.
49. Hogan, E.L., Lo, H.S., Power, J.M., et al.: Genetic deficiency of myoadenylate deaminase. IV International congress on Neuromuscular Diseases. 517 (abstract), 1978.
50. Hogan, G.R., Gutman, L., Schmidt, R., et al.: Pompe's disease Neurology, *19*:894–900, 1969.
51. Hohn, A.R., Lowe, C.U., Sokol, J.E., et al.: Cardiac problems in the glycogenoses with specific reference to Pompe's Disease. Pediatrics, *35*:313–321, 1965.
52. Hostetler, K.Y., Hoppel, C.L., Romine, J.S., et al.: Partial deficiency of muscle carnitine palmitoyltransferase with normal ketone production. New Eng. J. Med., *298*:553–557, 1978.
53. Hudgson, P., Gardner-Medwin, D., Worsfold, M., et al.: Adult myopathy from glycogen storage diseases due to acid maltase deficiency. Brain, *91*:435–461, 1968.
54. Hudgson, P., and Fulthorpe, J.J.: The pathology of type II skeletal muscle glycogenosis: A light and electron microscopic study. J. Pathol., *116*:139–147, 1975.
55. Isaacs, H., Heffron, J.J.A., Badenhorst, M., et al.: Weakness associated with the pathological presence of lipid in skeletal muscle: A detailed study of a patient with carnitine deficiency J. Neurol. Neurosurg. Psychiatry, *39*:1114–1123, 1976.
56. Jerusalem, F., Spiess, H., and Baumgartner, G.: Lipid storage myopathy with normal carnitine levels. J. Neurol. Sci., *24*:273–282, 1975.
57. Karpati, G., Carpenter, S., Engel, A.G., et al.: The syndrome of systemic carnitine deficiency. Neurology (Minneap.), *25*:16–24, 1975.
58. Karpati, G., Carpenter, S., Eisen, A., et al.: The adult form of acid maltase (α-1,4 glucosidase) deficiency. Ann. Neurol., *1*:276–280, 1977.
59. Layzer, R.B., Rowland, L.P., and Ranney, H.M.: Muscle phosphofructokinase deficiency. Arch. Neurol., *17*:512–523, 1967.
60. Layzer, R.B., and Rowland, L.P.: Cramps. New Engl. J. Med., *285*:31–40, 1971.

61. Layzer, R.B., and Rasmussen, J.: The molecular basis of muscle phosphofructokinase deficiency. Arch. Neurol., *31*:411–417, 1974.
62. Layzer, R.B., Havel, R.J., Becker, N., et al.: Muscle carnitine palmityltransferase deficiency: A case with diabetes and ketonuria. Neurology (Minneap.), 27:379–380, 1977.
63. Markesbery, W.R., McQuillen, M.P., Procopis, P.G., et al.: Muscle carnitine deficiency: Association with lipid myopathy, vacuolar neuropathy and vacuolated leukocytes. Arch. Neurol., *31*:320–324, 1974.
64. Martin, J.J., deBarsy, T., and denTandt, W.R.: Acid maltase deficiency in non-identical adult twins. J. Neurol., *213*:105–118, 1976.
65. McArdle, B.: Myopathy due to a defect in muscle glycogen breakdown. Clin. Sci., *10*:13–35, 1951.
66. Mastaglia, F.L., McCollum, J.P.K., Larson , P.F., et al.: Steroid myopathy complicating McArdle's disease. J. Neurol. Neurosurg. Psychiatry, 33:111–120, 1970.
67. Mehler, M., and DiMauro, S.: Late-onset acid maltase deficiency. Detection of patients and heterozygotes by urniary enzyme assay. Arch. Neurol, 33:692–695, 1976.
68. Mehler, M., and DiMauro, S.: Residual acid maltase activity in late onset acid maltase deficiency. Neurology, 27:178–184, 1977.
69. Meienhofer, M.C., Askanas, V., Proux-Daegelen, D., et al.: Muscle type phosphorylase activity present in muscle cells cultured from three patients with myophosphorylase deficiency. Arch. Neurol., *34*:779–781, 1977.
70. Munsat, T.L.: A standardized forearm ischemic exercise test. Neurology, *20*:1171–1178, 1970.
71. Murase, T., Ikeda, H., Muro, T., et al.: Myopathy associated with type III glycogenosis. J. Neurol. Sci., *20*:287–295, 1973.
72. Niermeijer, M.F., Koster, J.F., Jahodova, M., et al.: Prenatal diagnosis of type II glycogenosis (Pompe's disease) using microchemical analyses. Pediatr. Res., *9*:498–503, 1975.
73. Oliner, J., Schulman, M., and Larner, J.: Myopathy associated with glycogen deposition resulting from generalized lack of amylo-1, 6-glucosidase. Clin. Res., *9*:243, 1961.
74. Osame, M., Iwamasa, T., Kowabuchi, M., et al.: Familial muscle type amylo-1,6-glucosidase deficiency. IV International Congress on Neuromuscular diseases. 207 Abstract) 1978.
75. Özand, P., Tokatli, M., and Amiri, S.: Biochemical investigations of an unusual case of glycogenosis. Deficient hepatic glucose-6-phosphatase and muscle amylo-1,6-glucosidase with severe myopathy. J. Pediatr., *71*:225–232, 1967.
76. Pearson, C.M., Rimer, D.G., and Mommaerts, W.F.H.M.: A metabolic myopathy due to absence of muscle phosphorylase. Amer. J. Med., *3*:502–517, 1961.
77. Pernow, B.B., Havel, R.J., and Jennings, D.B.: The second wind phenomenon in McArdle's syndrome. Acta Med. Scand., *472*:294–307, 1967.
78. Roelofs, R.I., Engels, W.K., and Chauvin, P.B.: Histochemical phosphorylase activity in regenerating muscle fibers from myophosphorylase-deficient patients. Science. *177*:795–797, 1972.
79. Rowland, L.P., Fahn, S., and Schotland, D.L.: McArdle's disease: Hereditary myopathy due to absence of muscle phosphorylase. Arch. Neurol., *9*:325–342, 1963.
80. Rowland, L.P., Araki, S., and Carmel, P.: Contracture in McArdle's disease. Stability of adenosine triphosphate during contracture in phosphorylase-deficient human muscle. Arch. Neurol., *13*:541–544, 1965.
81. Rowland, L.P., Lovelace, R.E., Schotland, D.L., et al.: The clinical diagnosis of McArdle's disease. Neurology (Minneap.), *16*:93–100, 1966.
82. Rowland, L.P.: Glycogen storage diseases of Muscle. *In* Goldensohn, E.S., and Appel, S.H., eds.: Scientific Approaches to Clinical Neurology. Philadelphia, Lea and Febiger, Philadelphia, 1977. Volume II, pp. 1692–1714.
83. Sahn, L., and Magee, K.R.: Phosphorylase deficiency associated with isometric exercise intolerance. Neurology, *26*:896–898, 1976.
84. Satoyoshi, E., and Kowa, H.: A myopathy due to glycolytic abnormality. Arch. Neurol., *17*:248–256, 1967.
85. Schimrig, K., Metens, H.G., Ricker, K., et al.: McArdle's syndrome (Myopathie bei fehlender Muskelphosphorylase). Klin. Wochenschr., *45*:1–17, 1967.
86. Schmid, R., and Mahler, R.: Chronic progressive myopathy with myoglobin-uria. Demonstration of a glycogenolytic defect in the muscle. J. Clin. Invest., *38*:2044–2058, 1959.
87. Schmid, R., and Hammaker, L.: Hereditary absence of muscle phosphorylase (McArdle's syndrome). New Eng. J. Med., *264*:223–225, 1961.
88. Schochet, S.S., McCormick, W.F., and Zellweger, H.: Type IV Glycogenosis (amylpectinosis). Light and electron-microscopic observations. Arch. Pathol., *90*:354–363, 1970.

89. Schochet, S.S., McCormick, W.F., and Kovarsky, J.: Light and electron microscopy of skeletal muscle in Type IV glycogenosis. Acta Neuropathol. (Berl.), *19*:137–144, 1971.
90. Schotland, D.L., Spiro, D., Rowland, L.P., et al.: Ultrastructural studies of muscle in McArdle's disease. (Deficiency of muscle phosphorylase.) J. Neuropathol. Exper. Neurol., *24*:629–644, 1965.
91. Scholte, H.R., Jennekens, F.G.I., Bouvy, J.J.B.J.: Deficient carnitine palmitoyltransferase II in skeletal muscle, leukocytes and fibroblasts. IV International Congress on Neuromuscular Diseases. 204 (Abstract) 1978.
92. Serratrice, G., Monges, A., Roux, H., et al.: Forme myopathique du deficit en phosphofructokinase. Rev. Neurol., *120*:271–277, 1969.
93. Smith, J., Zellweger, H., and Afifi, A.K.: Muscular form of glycogenosis, type II (Pompe). Neurology (Minneap.), *17*:537–549, 1967.
94. Smyth, D.P.L., Lake, B.D., MacDermot, J., et al.: Inborn error of carnitine metabolism ("carnitine deficiency") in man. Lancet, *1*:1198–1199, 1975.
95. Swaiman, K.F., Kennedy, W.R., and Sauls, H.S.: Late infantile acid maltase deficiency. Arch. Neurol., *23*:642–648, 1968.
96. Tarui, S., Okuno, G., Ikura, Y., et al.: Phosphofructokinase deficiency in skeletal muscle. A new type of glycogenosis. Biochem. Biophys. Res. Commun., *19*:517–523, 1965.
97. Tobin, W.E., Huijing, F., Porro, R.S., et al.: Muscle phosphofructokinase deficiency. Arch. Neurol., *28*:128–130, 1973.
98. Vandyke, D.H., Griggs, R.C., Markesbery, W., et al.: Hereditary carnitine deficiency of muscle. Neurology, *25*:154–159, 1975.
99. Van Hoof, F., and Hers, H.G.: The subgroups of type III glycogenosis. Eur. J. Biochem., *2*:265–270, 1967.
100. Zellweger, H., Illingworth-Brown, B., McCormick, W.F., et al.: A mild form of muscular glycogenosis in two brothers with alpha-1,4-glucosidase deficiency. Ann. Paediat., *205*:413–437, 1965.
101. Zellweger, H., Mueller, S., Ionescu, V., et al.: Glycogenosis IV. A new cause of infantile hypotonia. J. Pediatr., *80*:842–844, 1972.

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Neurological Complications of Systemic Cancer

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Cancer is a common disease and the nation's second leading cause of death. Current estimates suggest that one out of four people will suffer from cancer at some time and that each year there are 690,000 new cases of cancer and 385,000 deaths.[26]. Although cancer *arising* in the central nervous system (brain or spinal cord) accounts for only about 2 per cent of all cancers (there are about 11,000 malignant primary brain tumors in the United States per year), neurological disability occurring in patients with other cancers is common. As many as 15 per cent of patients suffering from systemic cancer develop neurological symptoms which are either a direct or an indirect effect of the underlying disease. The physician encounters such patients with cancer and neurological disease in two settings. In the first, a patient known to have cancer presents with neurological disability. The physician's task is to determine: (1) whether the neurological abnormality is related to the cancer or is a separate and coincidental illness, and (2) if related to the cancer, from which of a bewildering variety of metastatic and nonmetastatic complications of cancer his patient suffers. In the converse of the above problem, the physician encounters a patient with a neurological abnormality who is not known to have cancer. The physician must determine the likelihood that the patient's clinical symptoms and signs are related to cancer and how extensively he should search for an occult neoplasm. Neither problem is trivial. Although many patients suffering from neurological complications of systemic cancer have incurable disease, *accurate diagnosis and appropriate treatment of neurological complications often prolong life and improve its quality.* This essay attempts to classify the various neurological complications of systemic cancer and to indicate some of the problems in differential diagnosis. Treatment is dealt with elsewhere.[10, 18, 19]

Systemic neoplasms can affect the nervous system in one of two

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Table 1. *Neurologic Dysfunction Caused by Systemic Cancer*

Metastatic
Intracranial
Spinal
Leptomeningeal
Peripheral nervous system
Nonmetastatic
Metabolic encephalopathy
Central nervous system infections
Vascular disorders
Side-effects of therapy
Paraneoplastic syndrome ("remote effects")

ways (Table 1): The tumor may metastasize to the nervous system, or the tumor may cause nervous system dysfunction indirectly. In the case of metastases, the various abnormalities can be subdivided anatomically into intracranial metastases (usually in the brain itself — occasionally in the epidural or subdural space), spinal metastases (usually epidural), leptomeningeal metastases, and metastases to peripheral nerves (particularly brachial and lumbosacral plexus, but also cranial nerves exiting from skull). Nonmetastatic complications are best subdivided pathophysiologically and include metabolic encephalopathy, infections, vascular disorders, side-effects of therapy, and paraneoplastic syndromes ("remote effects").

METASTASES

Brain Metastases

Metastasis to the brain is the most common metastatic complication of systemic cancer. Autopsy studies suggest as many as 15 per cent of patients who die of cancer harbor brain metastases at autopsy.[20] Of these, two-thirds to three-quarters will have suffered some neurological symptom during life. Many will have been disabled by neurologic disease and have died as a direct result of the metastasis. There is some evidence that as patients with systemic cancer are living longer (a result of vigorous radiation and chemotherapy), both the frequency of brain metastasis and its clinical importance to the patient is increasing.

Most metastases reach the brain hematogenously via the arterial circulation. This fact implies both that pulmonary cancer will be an important source of brain metastasis (indeed, the commonest source),[20] and also, if the primary tumor is not pulmonary, that the tumor has probably metastasized to the lung before seeding the arterial circulation to reach the brain. Thus, a careful chest x-ray examination is an exceedingly fruitful diagnostic test; it will be positive in the vast majority of patients suffering brain metastases. In some instances when the plain chest x-ray film is negative, tomography of the

lungs will reveal metastases and suggest the cause of the neurological disorder. In the few patients with brain metastases but no identifiable lesions in the lung, the pathogenesis of the brain metastases may be: (1) spread via Batson's plexus, the epidural collection of veins that potentially connects pelvic and intracranial structures, (2) a tumor embolus through a patent foramen ovale, or (3) tumor filtered through the lungs without local growth or only microscopic growth in the lung.

Brain metastases appear anywhere within the brain. The distribution generally parallels the blood supply to the brain (Fig. 1). Thus, metastases occur about equally in both hemispheres, with about 10 to 15 per cent in the cerebellum and 2 to 3 per cent in the brainstem.[20] In about half the patients with brain metastases, the lesions are multiple. Multiple brain lesions are more common with certain tumors, such as malignant melanoma (Fig. 2) and, to lesser degree, carcinoma of the lung. Metastases from colon carcinoma, carcinoma of the breast, and renal cell carcinoma are more often single.

Signs and Symptoms (Table 2)

In most patients, the neurological history of a brain metastasis is one of focal cerebral dysfunction, mild at onset but inexorably progressing to significant neurological disability within a few weeks. Headache is the commonest presenting symptom, occurring in about 50 per cent of patients, and generally beginning as a mild headache present on awakening but clearing after arising from bed. If untreated, the headache becomes more frequent and severe. Other important neurological symptoms include progressive weakness, changes in behavior and cognitive function, and, in about 15 per cent of patients, seizures as the presenting event. These signs and symptoms, which suggest a progressively enlarging mass, do not, if the patient is known to have cancer, give the physician much difficulty in diagnosis.

Once the diagnosis is suspected, a computed tomographic (CT) scan is the laboratory diagnostic test of choice.[4] The scan should be

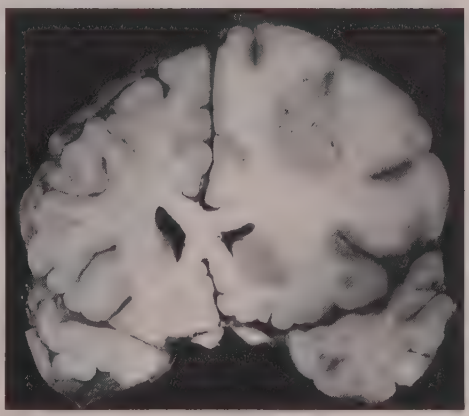

Figure 1. A single metastatic brain tumor surrounded by edema. Most metastatic brain tumors arise at the junction between the gray and white matter and produce a considerable amount of swelling in the surrounding white matter.

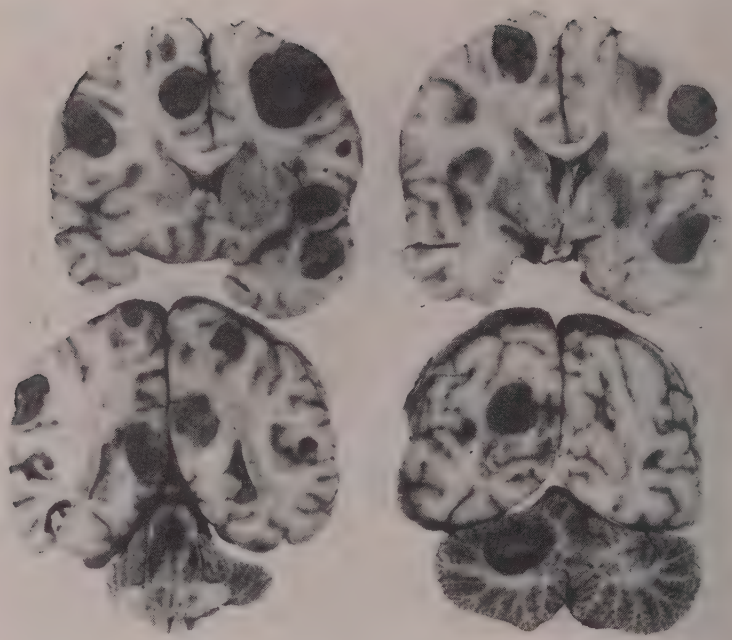

Figure 2. Malignant melanoma with multiple brain metastases.

performed both before and after the intravenous injection of contrast material. Some metastatic tumors, particularly malignant melanoma and carcinoma of the colon, are dense before the injection of contrast material. Others are lucent but enhance after contrast injection. The typical metastatic tumor is spherical and surrounded by edema. It either enhances solidly (Fig. 3) or, more commonly, develops a ring of contrast enhancement with a lucent center (Fig. 4). If the history is typical and the lesions are multiple, there is little doubt as to the diagnosis.

Table 2. *Presenting Symptoms and Signs of Brain Metastases (162 cases)*

SYMPTOMS	PERCENT OF PATIENTS	SIGNS	PERCENT OF PATIENTS
Headache	53	Hemiparesis	66
Focal weakness	40	Impaired cognitive function	77
Behavioral and mental change	31	Unilateral sensory loss	27
Seizures	15	Papilledema	26
Ataxia	20	Ataxia	24
Aphasia	10	Aphasia	19

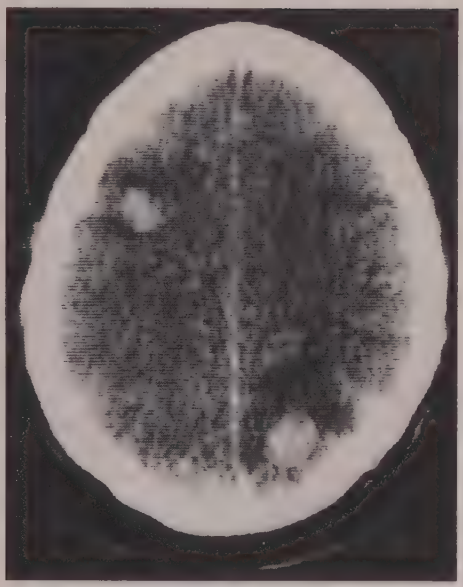

Figure 3. A CT scan with two contrast-enhanced cerebral metastases surrounded by edema. In this patient, the contrast enhancement is solid.

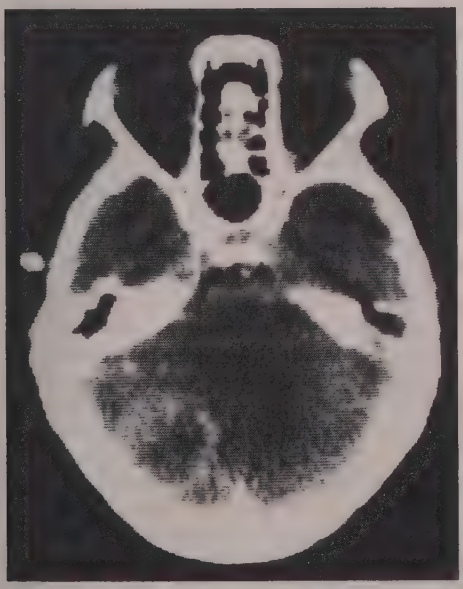

Figure 4. A cerebellar metastasis with ring-like contrast enhancement.

There are, however, pitfalls in the diagnosis of metastatic brain tumors, even when the patient is known to have cancer. An unusual clinical course may lead the physician to believe the patient is suffering from a neurological disease other than metastasis. About 5 to 10 per cent of patients with metastatic tumors present in an apoplectic manner, with the sudden onset of severe neurological disability (e.g., hemiplegia or aphasia). The physician may believe that his patient has suffered a stroke, but the CT scan should establish the correct diagnosis of a space-occupying lesion. The pathogenesis of an apoplectic onset is not certain. Some hypotheses are: (1) hemorrhage into the tumor, (2) occlusion by tumor of a cerebral blood vessel with brain infarction, (3) and a nonconvulsive seizure with profound postictal paralysis.[7] Even more perplexing is the patient who suffers the sudden onset of neurological disability followed by full recovery. The physician may believe he is dealing with a transient ischemic attack. The pathogenesis of these transient symptoms is likewise unknown. Hypotheses have included: (1) tumor embolization to the brain, causing transient ischemia, or (2) a "silent seizure" followed by a rapidly clearing postictal paralysis.[7] Another perplexing clinical picture is that of "dementia" without focal neurological signs. The patient presents with rapidly developing changes in behavior, judgment and memory, suggesting either a dementing illness or metabolic brain disease. This particular clinical picture generally occurs with patients who have multiple small cerebral metastases (often from oat cell carcinoma or malignant melanoma), and the CT scan usually establishes the diagnosis.

Even when the clinical findings *suggest* a brain metastasis and the CT scan is positive, the physician must consider other diagnostic possibilities. These include: (1) a second primary brain tumor, (2) a brain abscess, (3) cerebral infarct or hemorrhage. Primary gliomas of the brain, although usually single, are occasionally multiple. Primary brain tumors usually are less discrete and more infiltrating on CT scan than are metastatic tumors. Far more important is the correct diagnosis of a benign brain tumor. Meningiomas are more common in patients with carcinoma of the breast than in other women,[24] and should always be considered in the differential diagnosis of a patient with breast cancer and a potential brain metastasis. The CT scan usually reveals a single lesion on the surface of the brain which is dense before administration of contrast and strongly enhances afterwards.[4] If there is any doubt, cerebral arteriography, sometimes followed by craniotomy and biopsy, is required to differentiate the two.

A brain abscess must always be considered in the differential diagnosis of brain metastases.[3] Brain abscesses are rare in those systemic cancers which usually metastasize to the nervous system, i.e., lung cancer, melanoma, and breast cancer, and are more common in lymphomas (especially Hodgkin's disease, which rarely causes brain metastasis). Since brain abscesses (particularly toxoplasma abscesses) may be treatable, if there is any doubt, the lesions should be biopsied.

Cerebral vascular disease also complicates cancer, leading to intracranial hemorrhage and infarction.[23] These entities rarely cause diagnostic difficulties, but if the history and CT scan are not clear, cerebral arteriography is often helpful.

What about the patient with a brain metastasis who is not known to have cancer? The patient has usually presented with progressive neurological symptoms and the CT scan reveals one or more lesions in the brain. The questions are: is the lesion a tumor and, if so, is the tumor primary or metastatic? How extensive a search should be made for a primary cancer if the physician suspects the brain lesion is a metastatic tumor? Included in the physician's differential diagnosis is multiple sclerosis (multiple sclerosis can produce a contrast-enhancing lesion in the brain[9] but the lesion is not surrounded by edema and does not distort brain structures), brain abscess, primary brain tumor, and metastatic tumor. A multiplicity of lesions suggests metastases, as do well-circumscribed, spherical lesions surrounded by edema. However, often a definitive diagnosis cannot be made without a biopsy. Single lesions should probably be biopsied unless there is good evidence of systemic cancer; multiple lesions with the appropriate history and setting should be thoroughly investigated for a primary lesion before biopsy is considered.

Brain metastasis as the presenting complaint in the patient with cancer is not rare. Most surgical series of brain metastasis include 10 to 20 per cent of patients in whom the primary source is unknown.[22] Brain metastases of unknown primary source usually arise from the lungs. The kidney and gastrointestinal tract are also common sources. If a patient is suspected of having a metastatic lesion in the brain without a known primary lesion, the evaluation should include a chest x-ray, sputum cytology, intravenous pyelogram, and stool guaiac tests. Also likely to be fruitful are radionuclide bone scan (which may show other metastatic lesions easily accessible for biopsy), measurement of the serum tumor markers, including carcinoembryonic antigen and acid phosphatase, upper and lower gastrointestinal series, and a CT scan of the abdomen (looking for pancreatic carcinoma). However, even after an extensive search, the primary tumor is often not discovered,[22] and in these instances, biopsy or extirpation of a single cerebral metastasis appears warranted.

Spinal Cord Tumors

Epidural spinal cord compression by metastatic tumor is relatively common, perhaps affecting about 5 per cent of patients with systemic cancer at some time during their course. In some instances, epidural spinal cord compression is the first evidence that the patient is suffering from cancer. Metastatic tumor reaches the epidural space and compresses the spinal cord in one of two ways. In most instances, there is a metastasis to the vertebral body and the tumor grows into the epidural canal from the bony lesion. Less commonly (but characteristic of lymphomas and neuroblastomas), a paravertebral tumor grows into the spinal canal through an intravertebral foramen (Fig. 5). Rarely, there may be hematogenous metastasis directly to the epidural space. Hematogenous metastases to the parenchyma of the spinal cord have also been reported but are uncommon.

Figure 5. Epidural spinal cord compression from malignant lymphoma. In this patient, there was a complete block to the passage of myelographic contrast material at C4. There were no lesions on plain x-ray films or on bone scan. The tumor had grown from a paravertebral neck mass through the intervertebral foramen.

The characteristic history of epidural spinal cord compression has been described in detail elsewhere.[16] Typically, back pain, frequently exacerbated by coughing or sneezing, develops and grows progressively worse over several weeks. Radicular pain may also develop, either at the time the local back pain occurs or somewhat later. In the extremities, the radicular pain is usually unilateral. In the thoracic or upper lumbar regions it is usually bilateral, as if a tight band were constricting the thorax or abdomen. After a period of several weeks or months in which pain is the only symptom, neurological signs, including weakness, sensory loss, ataxia, and bladder and bowel dysfunction, then occur, usually evolving rapidly. In the typical patient, the diagnosis is suggested not only by the history but also by destructive lesions of the vertebral body on the plain x-ray film (about 85 per cent of patients). The diagnosis is confirmed by myelography (Fig. 5). The outcome of treatment is inversely proportional to the degree of disability before treatment is undertaken, and once complete paraplegia has occurred, the likelihood of a successful outcome is almost nil. Thus, early diagnosis and emergency treatment, whether by decompressive laminectomy or radiation therapy, is vital.[15, 21]

Diagnostic problems arise either because the pain is ignored by the patient or his physician, or the story is not typical. It is fairly common for a patient with widespread cancer suffering from pain in multiple areas of the body to neglect to inform the physician that a new pain in the neck or back has occurred, and it is all too common for the physician, if he is told of the pain, not to recognize its significance. Patients

with known cancer should be warned to report new pains promptly so that the physician can evaluate their import.

Other problems in diagnosis arise when the presentation is atypical. Five to 10 per cent of patients with epidural spinal cord compression producing neurological symptoms do not develop pain at any time in the course. In these cases, the picture is one of painless but progressive neurological disability. The physician may suspect that the myelopathy is the result of an unrelated disease (e.g., multiple sclerosis) or is a paraneoplastic illness. Since epidural spinal cord compression from metastasis is so common and the other diagnoses so much rarer, myelography is always necessary.

Even more perplexing is the occasional patient whose course is painless and whose symptoms are those of ataxia rather than weakness or sensory loss. We have encountered patients with such profound ataxia of the lower extremities that an initial diagnosis of cerebellar disease was made. The absence of symptoms suggesting cerebellar dysfunction above the foramen magnum (e.g., dysarthria, nystagmus), however, points to the spinocerebellar tracts. Myelography establishes the diagnosis.

Since spinal cord compression may be the presenting complaint of a cancer, the physician should always be alert to the possibility of systemic malignant disease in any middle-aged patient who presents for the first time with back pain. He should be particularly suspicious if the back pain is not relieved by bed rest and if it appears inexorably progressive. Spine films and a radionuclide bone scan should be procured early, and if there is evidence of vertebral destruction, a biopsy of the bone may establish the diagnosis of cancer. If neurological symptoms develop, myelography should be carried out promptly.

LEPTOMENINGEAL METASTASIS

The term leptomeningeal metastasis refers to diffuse or widespread multifocal seeding of the leptomeninges by systemic cancer.[14, 17] Once the leptomeninges have been invaded, the tumor spreads along subarachnoid pathways, probably carried by the flow of spinal fluid, to seed the subarachnoid space widely (Fig. 6). The sites of heaviest infiltration are usually within the cisterns at the base of the brain, in the Sylvian and hippocampal fissures, and around the cauda equina. Signs and symptoms of leptomeningeal metastases are produced in one of several ways: (1) there may be hydrocephalus and increased intracranial pressure from obstruction by tumor of the cerebrospinal fluid absorptive pathways, (2) there may be signs of focal brain or spinal cord dysfunction, including seizures, from direct invasion into the parenchyma (Fig. 6), (3) cranial nerves and spinal roots may be involved as they pass through the subarachnoid space.

The tumors which commonly cause leptomeningeal metastases are carcinomas of the breast and lung, lymphomas, and malignant melanomas. Meningeal leukemia from acute lymphocytic leukemia,

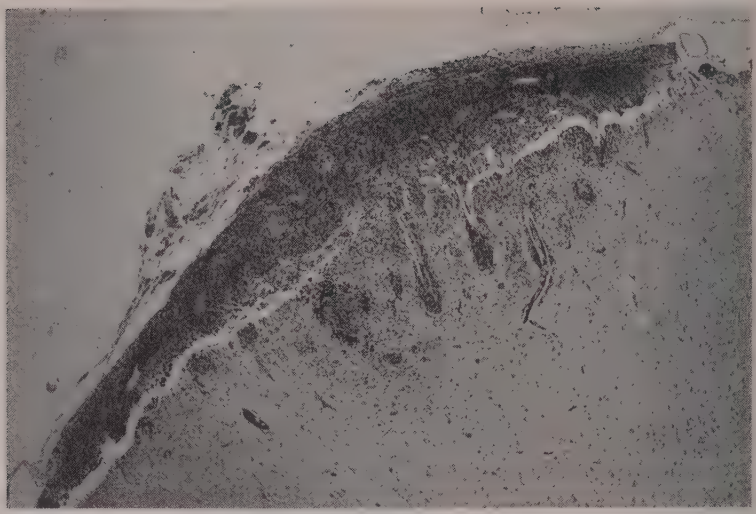

Figure 6. Leptomeningeal metastases. This is a section of cerebral cortex and overlying leptomeninges. The leptomeninges are heavily infiltrated with tumor. The tumor has surrounded penetrating blood vessels from the leptomeninges into the parenchyma of the brain.

formerly a common complication of this disorder, now is much rarer because of prophylactic treatment of the central nervous system.

Because the entire neuraxis can be seeded, the signs and symptoms may involve any part of the nervous system. A few clues lead one to suspect the diagnosis of leptomeningeal metastasis in patients known to be suffering from systemic cancer. The first is that the neurological symptomatology is more widespread than can be explained on the basis of a single lesion. For example, the patient may complain of diplopia resulting from ocular nerve dysfunction and also complain of weakness or numbness in one upper or lower extremity in a dermatomal distribution. The second clue is that although patients may have unifocal complaints, careful neurological examination often reveals neurologic signs unexplainable by a lesion at the site of the major complaint. Thus, for example, a patient with headache and papilledema suggesting increased intracranial pressure may on careful examination have an absent ankle jerk and weakness of plantar flexion of the foot, suggesting coexisting disease of sacral roots. The diagnosis of leptomeningeal metastasis is made by lumbar puncture. (A lumbar puncture can be dangerous in patients with brain tumors causing increased intracranial pressure. A CT scan should be performed first and the lumbar puncture performed only after treatment for the mass lesion has begun.) The cerebrospinal fluid in a patient suffering from leptomeningeal metastases is usually under increased pressure, with an increased number of lymphocytes (a reaction to the irritation of tumor in the meninges). The protein concentration is usually elevated, the glucose concentration may be depressed, and malignant cells can often be identified. If the first lumbar puncture is not diagnostic, at

least two or three more should be performed looking for malignant cells. The absence of malignant cells in the cerebrospinal fluid does not rule out leptomeningeal metastasis.

Sometimes leptomeningeal masses can be identified by myelography or CT scan (Fig. 7). The presence of malignant cells in the spinal fluid usually establishes the diagnosis of leptomeningeal metastasis since brain metastases not involving the subarachnoid space do not seed malignant cells into the cerebrospinal fluid.[8] The differential diagnosis includes infective meningitis: The cerebrospinal fluid should be cultured for bacteria and fungi, and fungal antigens assayed.

A more difficult problem arises when a patient not known to have cancer presents to the physician with a "chronic meningitis".[6] Here, in addition to leptomeningeal metastases, one must consider a variety of other disorders, including central nervous system sarcoidosis and bacterial and fungal infections. Careful evaluation of the cerebrospinal fluid for malignant cells as well as for cultural or antigenic evidence of invading organisms must be carried out. At times, meningeal biopsy is the only way of definitively establishing the diagnosis.

Metastases to Cranial or Peripheral Nerves, Roots, and Plexuses

The major diagnostic problem is in the diagnosis of upper extremity pain and dysfunction. In a patient known to have cancer who has

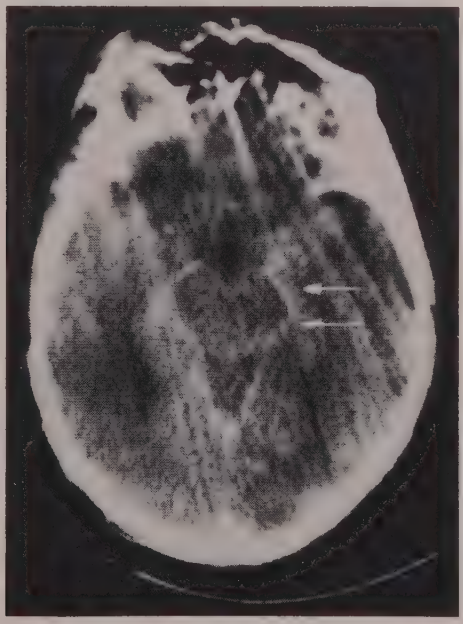

Figure 7. A contrast-enhanced CT scan in a patient with leptomeningeal metastases. In this patient, contrast enhancement of the basal cisterns (arrows) was instrumental in establishing the diagnosis of leptomeningeal metastases.

received radiation therapy to a port encompassing the brachial plexus, the development of progressive brachial plexus dysfunction months or years later may be due either to recurrence of tumor or to radiation damage. The diagnosis is often difficult,[12] but certain clues help. The typical patient with metastatic involvement of the brachial plexus presents with severe pain in the shoulder, usually radiating down the medial aspect of the arm to the elbow. The pain may radiate down the ulnar aspect of the forearm into the fourth and fifth fingers as well. Sensory loss and motor dysfunction develop in the lower cervical and upper thoracic root dermatomes (sensory loss begins in the fourth and fifth fingers and weakness in the small muscles of the hand). A Horner's syndrome is common. X-ray films may show a lung tumor, or destruction of the clavicle or the lower cervical and upper thoracic vertebral bodies. At myelography there is often an epidural mass.

In the patient with radiation fibrosis of the plexus, pain is usually less prominent or absent. Sensory loss and motor dysfunction are more prominent in the upper cervical roots, leading to numbness over the outer aspect of the arm and weakness of the shoulder girdle. Horner's syndrome is uncommon but lymphedema of the arm is common. X-ray films and myelograms are negative. Unfortunately, at times the clinical findings cannot differentiate the two lesions. Surgical exploration of the plexus may be helpful, revealing either tumor infiltrating the plexus or marked fibrosis of roots and the absence of tumor. However, even surgical exploration is not infallible. We have encountered several patients in whom the tumor was not located at the first exploration and became apparent only after the passage of months.

An entirely different problem is presented by the patient not known to have cancer who complains of pain and/or weakness in the upper extremity. Here the differential diagnosis includes a tumor involving the brachial plexus, cervical disc disease, and thoracic outlet syndrome. Several clues should help in this differentiation. Cervical disc disease usually involves the C5 and C6 roots, producing pain in the neck and shoulder, and numbness or paresthesias in the thumb and index finger. If there is weakness, it usually involves muscles of the shoulder girdle. Tumors involving the brachial plexus usually cause dysfunction of the C8 and T1, roots not commonly involved by cervical discs. Thoracic outlet syndromes, although involving the C8 and T1 roots, usually cause intermittent and mild pain and paresthesias rather than severe unrelenting pain and constant numbness. Significant sensory loss and motor weakness are unusual. A correct selection of x-ray studies is necessary to establish the diagnosis. Because it is often difficult to "see" C7 and T1 vertebral bodies on plain films (they are hidden by the shoulders), tomography may be necessary. Careful x-ray examination of the chest may reveal a lesion involving the apex of the lung. Myelography helps differentiate disc disease from tumor.

NONMETASTATIC COMPLICATIONS OF CANCER

Table 1 classifies nonmetastatic complications of systemic cancer. Although each may cause diagnostic problems, there are two areas in

which the physician encounters major problems: (1) separating side-effects of cancer therapy from metastatic disease of the nervous system, and (2) evaluating a patient with a paraneoplastic syndrome.

SIDE EFFECTS OF THERAPY

Whole-Brain Radiation Therapy

Radiation therapy directed at the brain can produce acute, subacute or chronic side-effects.[13] The acute symptoms present little diagnostic difficulty. They usually arise during the course of radiation therapy, and are easily attributable to the therapy. Acute cerebral symptoms include headache, photophobia, fever, and transient worsening of already present neurological signs. Other side-effects include acute parotitis, hyperamylasemia, loss of taste, dryness of the mouth, conjunctivitis, and occasionally serous otitis media. All of these side-effects are transient.

The nervous system may also be affected some weeks after the brain has been irradiated (subacute effects). Some children undergoing prophylactic radiation of the brain for acute lymphoblastic leukemia develop a syndrome characterized by headache, lethargy, somnolence, and sometimes nausea and vomiting 6 to 8 weeks after therapy. The syndrome, which probably also occurs in adults, may lead the physician to believe that the patient is developing metastatic disease of the central nervous system. Corticosteroids often hasten the resolution of these symptoms, which will resolve spontaneously even if untreated. The pathogenesis of this disorder is not known, but transient demyelination has been suggested. A similar syndrome may occur in patients receiving radiation therapy for a brain tumor. In this instance, there is temporary worsening of the original symptomatology. Here the physician is faced with a real dilemma. Is the patient suffering from a subacute radiation effect or has the tumor enlarged? CT scans sometimes help. Treatment with corticosteroids may alleviate the symptoms but not clarify the diagnosis. Waiting and watching gives the answer.

A rare subacute radiation effect of therapy has been described in some patients who received high-dose radiation to a port encompassing the brainstem (usually for a malignant lesion around the ear). Six to 10 weeks following radiation therapy, the patients developed severe brainstem signs suggesting a demyelinating disorder. One patient who died had demyelinating lesions in the brainstem; the others recovered.

Chronic side-effects of radiation therapy usually begin a year or more following the cessation of therapy. In many patients, asymptomatic cerebral atrophy is evident on CT scan. A few may develop necrosis of the brain. The signs and symptoms of radiation necrosis frequently suggest recurrence of the original lesion, and biopsy may be required for diagnosis. If the area of radiation necrosis is focal, surgical extirpation of that area often produces amelioration of symptoms.

Radiation Myelopathy

Radiation myelopathy occurs in both subacute and chronic forms. The subacute form begins 6 to 10 weeks after radiation therapy to the

neck and is characterized by Lhermitte's sign, an electric shock-like sensation running down the back and into the extremities when the neck is flexed. The pathogenesis of Lhermitte's sign is probably demyelination of the dorsal columns. The sign persists for several weeks and usually disappears. There is no treatment, nor is any necessary.

Chronic radiation myelopathy occurs months to years following radiation therapy and is usually characterized by the painless onset of a Brown-Sequard syndrome (ipsilateral upper motor neuron weakness with contralateral loss of pin and temperature sensation). The disease is not always painless, however, and at times radicular pain suggests the presence of metastatic spinal cord compression rather than nonmetastatic myelopathy. The illness is usually progressive, although at times patients stabilize and rarely improve spontaneously. All patients suspected of radiation myelopathy must undergo myelography to rule out spinal cord compression since an unequivocal clinical diagnosis cannot be made. The myelogram is usually normal, although sometimes early in the course the spinal cord is enlarged. Occasionally the swelling is so severe that there is a complete block to the passage of myelographic contrast material. Later the spinal cord may become atrophic. Steroids have been reported to be helpful in slowing progression of the illness.

Chemotherapy

Several chemotherapeutic agents, including the vinca alkaloids, produce a peripheral neuropathy. The neuropathy is often painless, and consists of symmetrical distal sensorimotor impairment with absent reflexes. At times, however, neuropathy may be quite asymmetrical, suggesting the possibility that single nerves are compressed by tumor. A major problem is separating drug-induced peripheral neuropathy from leptomeningeal metastasis. The cerebrospinal fluid is usually normal in patients suffering from drug-induced peripheral neuropathy, and virtually always abnormal in the patients with leptomeningeal metastasis.

Another side-effect of chemotherapy is a leukoencephalopathy (destruction of white matter of the brain) caused by methotrexate. This disorder arises in several settings. It occasionally occurs in patients being treated with intrathecal methotrexate (for leptomeningeal tumor) over long periods of time. The disease may present either as a progressive myelopathy or as an encephalopathy with bilateral neurological signs including memory loss and cognitive dysfunction.[1] It also occurs in patients whose brains have been irradiated and who are receiving intravenous methotrexate in standard doses. The third setting is that of high-dose intravenous methotrexate for the treatment of systemic tumors *without* prior whole-brain irradiation. In this setting, progressive bilateral signs, including dementia, usually develop. One may see attenuation of white matter on CT scans. When the drug is stopped, the patient sometimes improves, although the CT scan remains abnormal and ventriculomegaly may ensue.

Paraneoplastic Syndromes

Paraneoplastic syndromes[27] or "remote effects" of cancer on the nervous system are nervous system abnormalities occurring exclusively or in higher incidence in patients harboring malignant systemic tumors *and not caused by metastatic invasion of the nervous system or by one of the identifiable nonmetastatic effects of cancer on the nervous system.* In about 50 per cent of instances, the nervous system symptoms precede the discovery of cancer and usually run a course independent of the tumor. The etiology of these disorders is unknown, although opportunistic viral infections, antigen-antibody reactions, and toxins produced by the tumor have all been suggested. The clinical problem is twofold: Either the patient is known to have cancer, and the question is whether the neurological symptoms are due to a remote effect or to metastatic disease; or the patient is not known to have cancer, and the questions are: Does the neurological picture suggest a paraneoplastic syndrome? Must the patient be carefully evaluated for an occult cancer? In the first instance, remote effects are so rare and metastatic disease so common, that in the patient with known cancer, the physician is obligated to consider and rule out all of the other neurological complications of systemic cancer before arriving at the conclusion that the patient's symptoms are paraneoplastic in origin.

Neurological symptoms which may cause diagnostic difficulty include dementia, cerebellar dysfunction, and weakness of the extremities. Dementia, particularly with memory loss, is one of the well-described remote effects of cancer on the nervous system. Similar symptoms, however, may occur in patients with multiple cerebral metastases or in patients with leptomeningeal metastases. The former are usually visible on CT scan and with the latter, one often sees hydrocephalus on CT scan and there are cerebrospinal fluid abnormalities. Furthermore, if the patient has become acutely demented, metabolic brain disease (e.g., hypercalcemia or liver failure) is a possible diagnosis. In patients with lymphoma, infections of the nervous system including progressive multifocal leucoencephalopathy and fungal meningitis must also be considered.

If cerebellar dysfunction develops in a patient with a known cancer, it is more likely that the patient is suffering from a metastasis in the cerebellum than from a remote effect. Clinically, subacute cerebellar degeneration as a remote effect is characterized by bilateral appendicular signs (point to point test difficulties with both upper and lower extremities) and by dysarthria, usually without nystagmus. Dementia is common as well. Metastatic disease of the cerebellum usually either causes difficulties in gait without involvement of the upper extremities or speech (midline lesion) or causes unilateral ataxia without gross dysarthria (hemispheral lesion). A CT scan usually establishes the diagnosis.

The most serious diagnostic problems arise in patients developing

weakness of the lower extremities with absent reflexes and with or without bladder or bowel dysfunction. The physician may suspect a paraneoplastic peripheral neuropathy, but the invasion of the cauda equina by leptomeningeal tumor is more likely. The diagnosis can usually be established by careful examination of cerebrospinal fluid.

Most paraneoplastic neurological diseases, such as sensorimotor peripheral neuropathy, dementia, and acute transverse myelopathy, occur only slightly more commonly in patients with cancer than in the general population. In such patients, a careful search for an underlying neoplasm is unlikely to be fruitful and is probably not warranted. Several neurological syndromes, however, occur exclusively or with much higher frequency in patients with cancer. These syndromes include dermatomyositis in middle-aged or elderly men,[5] subacute cerebellar degeneration,[2] subacute sensory neuropathy,[11] and a subacute motor neuronopathy.[25] Any patient presenting with one of the above neurological syndromes deserves a careful search for occult neoplasia. If the initial search is negative, a tumor should still be suspected until a definitive diagnosis is established. The search for tumor should include chest x-ray films and sputum cytology, careful pelvic examination, intravenous pylogram, upper and lower gastrointestinal series, and measurement of the serum for biochemical abnormalities and tumor markers.

Dermatomyositis[27] (polymyositis) is characterized by the subacute development of proximal muscular weakness, with or without pain and muscle tenderness, but usually associated with a skin rash. When it occurs in men over 40, there is a high incidence of underlying cancer, particularly carcinoma of the lung and a search for cancer is warranted.

Subacute cerebellar degeneration[2] is characterized by subacutely developing symmetrical ataxia of arms and legs, usually associated with dysarthria and sometimes associated with nystagmus. The cerebrospinal fluid may contain 10 to 40 lymphocytes and increased protein. The disorder is usually inexorably progressive. Carcinomas of the lung and ovary lead the list of those responsible for this remote effect. Occasionally the subacute cerebellar degeneration is associated with opsoclonus (i.e., rapid, chaotic, uncontrollable movement of the eyes.)

Subacute sensory neuropathy[11] is characterized by the progressive loss of all sensory modalities and the deep tendon reflexes in the four extremities. Because of loss of proprioception, ataxia is common. Motor power may be unimpaired and motor nerve conduction velocities may be normal. Many patients are mildly demented, and the cerebrospinal fluid protein is usually elevated. This syndrome, when severe, warrants a very careful search for an underlying neoplasm.

Subacute neuronopathy[25] is associated with lymphoma and is characterized by gradual lower motor neuron weakness, usually without sensory changes, which waxes and wanes over months and generally improves spontaneously. The patients frequently recover after several months to years. The etiology is unknown, although viral infection has

been postulated as a potential cause. Patients with Hodgkin's disease and lymphoma have a higher incidence of acute polyneuritis (the Guillain-Barré syndrome) than does the general population. However, the Guillain-Barré syndrome is so common and its association with lymphoma sufficiently rare, that the diagnosis of this neurological disorder does not require that the physician search for an underlying neoplasm.

REFERENCES

1. Allen, J.C.: The effects of cancer therapy on the nervous system. J. Pediatr., *93*:903–909, 1978.
2. Brain, W.R., and Norris, F.H., Jr.: The Remote Effects of Cancer on the Nervous System. New York, Grune & Stratton, 1965.
3. Chernik, N.L., Armstrong, D., and Posner, J.B.: Central nervous system infections in patients with cancer. Medicine, *52*:563–581, 1973.
4. Deck, M.D.F.: Computed tomography of metastatic disease of the brain. *In* Gilbert, H.A., Posner, J.B., Weiss, L. (eds): Brain Metastasis. Boston, GK Hall, 1979.
5. Devere, R., and Bradley, W.G.: Polymyositis: Its presentation, morbidity and mortality. Brain, *98*:637–666, 1975.
6. Ellner, J.J., and Bennett, J.E.: Chronic meningitis: Medicine, *55*:341–369, 1976.
7. Fisher, C.M.: Transient paralytic attacks of obscure nature: the question of nonconvulsive seizure paralysis. J. Canad. Sci. Neurol., *5*:267–273, 1978.
8. Glass, J.P., Melamed, M., Chernik, N.L., et al.: Malignant cells in cerebrospinal fluid (CSF): the meaning of a positive CSF cytology. Neurology (in press).
9. Hershey, L.A., Gado, M.H., and Trotter, J.L.: Computerized tomography in the diagnostic evaluation of multiple sclerosis. Ann. Neurol., *5*:32–39, 1979.
10. Hildebrand, J.: Lesions of the nervous system in cancer patients. European Organization for Research of Treatment of Cancer Monograph Series, Vol. 5 New York, Raven Press, 1978.
11. Horwich, M.S., Cho, L., Porro, R.S. et al.: Subacute sensory neuropathy: a remote effect of carcinoma. Ann. Neurol., *1*:7–19, 1977.
12. Kori, S.H., Foley, K.M., and Posner, J.B.: Brachial plexus lesions in patients with cancer: clinical findings in 100 cases. Neurology (in press).
13. Kramer, S., and Lee, K.F.: Complications of radiation therapy: the central nervous system. Sem. Roentgen., *9*:75–83, 1974.
14. Little, J.R., Dale, A.J.D., and Okazaki, H.: Meningeal carcinomatosis, clinical manifestations. Arch. Neurol., *30*:138–143, 1974.
15. Livingston, K.E., and Perrin, R.G.: The neurosurgical management of spinal metastases causing cord and cauda equina compression. J. Neurosurg., *49*:839–843, 1978.
16. Nystrom, J.S., Weiner, J.M., Wolf, R.M., et al.: Identifying the primary site in metastatic cancer of unknown origin. J.A.M.A., *241*:381–384, 1979.
17. Olson, M.E., Chernik, N.L., and Posner, J.B.: Infiltration of the leptomeninges by systemic cancer: a clinical and pathologic study. Arch. Neurol., *30*:122–137, 1974.
18. Posner, J.B.: Brain metastasis; a clinician's view. *In* Gilbert, H.A., Posner, J.B., and Weiss, L. (eds): Brain Metastasis. Boston, GK Hall, 1979.
19. Posner, J.B.: Neurological complications of systemic cancer. Disease-A-Month, 25:1–60, 1978.
20. Posner, J.B., and Chernik, N.L.: Intracranial metastases from systemic cancer. Adv. Neurol., *19*:575–587, 1978.
21. Posner, J.B., and Gilbert, R.W.: Epidural spinal cord compression from metastatic tumor. Ann. Neurol., *3*:40–51, 1978.
22. Ransohoff, J.: Surgical management of metastatic tumors. Sem. Oncol., 2:21–27, 1975.
23. Reagan, T.J., and Okazaki, H.: The thrombotic syndrome associated with carcinoma, a clinical and neuropathologic study. Arch. Neurol., *31*:390–395, 1974.
24. Schoenberg, B.S., Christine, B.W., and Whisnant, J.P.: Nervous system neoplasms and primary malignancies of other sites. The unique association between meningiomas and breast cancer. Neurology, *25*:705–712, 1975.
25. Schold, S.C., Cho, E-S., Somasundaram, M., et al.: Subacute motor neuronopathy: a remote effect of lymphoma. Ann. Neurol. (in press).

26. Silberberg, E.: Cancer statistics 1977. Ca-A Cancer Journal for Clinicians, 27:26–41, 1977.
27. Tyler, H.R.: Paraneoplastic syndromes of nerve, muscle and neuromuscular junction. *In* Hall, T.C., ed: Paraneoplastic Syndromes. Ann. N.Y. Acad. Sci., 230:348–357, 1974.
28. Weiss, H.D., Walker, M.D., and Wiernik, P.H.: Neurotoxicity of commonly used antineoplastic agents. New Eng. J. Med., 291:75–81, 127–133, 1974.

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Epilepsy: Mechanisms and Therapy

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Epilepsy is a disorder of the brain characterized by recurring seizures. The essence of an epileptic seizure is an abnormal and excessive discharge of nerve cells within the brain, which is manifested clinically or electrically, or both. The clinical manifestation of seizures depends on the number and location of discharging neurons. When relatively few motor cortex neurons discharge, there may be only jerking of a contralateral limb, without loss of consciousness (a simple partial seizure). When millions of neurons throughout the brain discharge, loss of consciousness is accompanied by a tonic-clonic phase, and these are followed by postictal confusion as consciousness gradually returns (a generalized tonic-clonic or grand mal seizure). In the former case of these two extremes, the patient is able to give a clear history of what happened; in the latter, there is no memory of the event, and the history must be obtained from observers. Between these two extremes are many different types of generalized or partial (focal) epileptic seizures.[2] The most prevalent type is the complex partial (psychomotor; temporal lobe) seizure. Occurring frequently and dramatically is the complex partial seizure with psychomotor symptomatology, characterized by amnesia, unresponsiveness, and semipurposeful movement or walking in a fugue-like state. On the other hand, subjective manifestations, such as hallucinations or distorted perceptive experiences (for example, micropsia), also occur in complex partial seizures.

The electrical manifestations of seizures are recorded by the electroencephalograph. The abnormal activity of cortical neurons during seizures is documented by the epileptiform discharges that appear on the electroencephalogram. Such abnormal discharges occur, with rare exceptions, during all seizures and many originate from structures deep within the brain. The well-known staring spells of childhood (absence or petit mal seizures) are associated with generalized 2 to 4/sec

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spike and wave discharges recorded from all areas of the scalp. Generalized tonic-clonic seizures are characterized by persistent, high voltage, generalized, irregular spikes. Complex partial seizures are usually initiated by spikes or spike and waves recorded from the temporal lobe or other areas of the brain and followed by generalized, irregular slowing. Unfortunately, the electroencephalogram is usually recorded interictally, when the patient is not having an epileptic seizure and may feel normal. Patients who have recurring seizures will show interictal abnormalities in more than half of the recordings.

Epilepsy is a serious public health problem: more than two million Americans have suffered two or more epileptic seizures, and more than four million have had at least one seizure. More than 200,000 Americans have seizures more than once a month despite treatment with antiepileptic drugs. The majority of epileptic seizures can be controlled if the correct seizure diagnosis is made and the correct drug is maintained at a therapeutic serum concentration. More than a third of epileptic patients have an underlying lesion of the brain that requires appropriate treatment if antiepileptic drugs are to be maximally effective.

Seizures are caused by hyperexcitable neurons. The variety of both experimental and clinical seizures attests to the many different ways in which such neurons and their connections may exist and express themselves. The discussion of seizure mechanisms will first concentrate on experimental data and then on clinical clues to the causes of seizures.

EXPERIMENTAL SEIZURES AND MECHANISMS

Virtually all we know about the basic mechanisms of seizures is derived from animal studies; two major reviews will serve as basic references.[9, 11] We have learned much, for example, from the effects of convulsants, drugs that are used to cause seizures, in animal models. Although many of these compounds have unknown or nonspecific actions, the mechanisms of action of certain convulsants are generally well defined. These compounds appear to act either by increasing excitability processes or by decreasing inhibitory processes. One example is the anticholinesterases, such as those found in some insecticides. By interfering with the breakdown of acetylcholine, a putative excitatory transmitter, the anticholinesterases cause an accumulation of this excitatory substance, which leads to increased neuronal firing and generalized seizures. Other convulsants, such as picrotoxin and bicuculline, act on a different brain substance, gamma aminobutyric acid (GABA), an inhibitory neurotransmitter. These drugs block the interaction of GABA with its receptors at presynaptic and postsynaptic inhibitory sites; the resulting decreased inhibition causes neuronal excitation and seizures. Other drugs may affect GABA and cause seizures in a different manner. Allylglycine, for example, causes a marked decrease in GABA concentration by interfering with its synthesizing enzyme, glutamic acid decarboxylase. Tetanus toxin causes hyperexcit-

ability in the spinal cord by interfering with the nerve terminal release of inhibitory transmitters such as GABA.

Other drugs cause seizures by interfering with metabolic processes; two examples are monofluoroacetic acid, which partially blocks the Krebs cycle, and deoxyglucose, which blocks utilization of glucose by neurons. Other convulsants, such as ouabain, inhibit active transport of ions through neuronal membranes, causing depolarization and leading to neuronal hyperactivity and seizures.

Although the relationship between these drugs and clinical seizures remains unclear, one drug may cause different types of seizures experimentally, depending on its mode of administration. Penicillin given to cats intraperitoneally causes generalized attacks resembling absence seizures in human beings. When applied directly to the cortex, however, penicillin causes an epileptic focus, as in partial seizures. Local epileptogenesis is a property shared with many other compounds, such as cobalt and alumina gel; it may also be caused by cortical freezing and other insults.

The epileptic neuron has been intensively studied in focal cortical seizure models. Its major physiologic abnormality is a tendency to "recurrent, high-frequency bursts of action potentials."[9] Wyler et al.[12] studied the population of epileptic neurons in monkeys and found a highly significant relationship between the number of such neurons in a focus and the frequency of epileptic attacks in the animal. These findings suggested that the attack frequency in focal epilepsy is directly related to the amount of epileptic tissue present. It is this abnormal tissue that recruits normal neurons, leading to propagation of the discharge and ultimately to the clinical seizure.

Experimental seizure models are also beginning to further our comprehension of the effects of seizures themselves. Although clinicians have long thought that chronic, frequent, generalized tonic-clonic seizures with attendant anoxia may cause permanent damage to brain cells, new evidence suggests that the developing brain may be especially vulnerable to the metabolic consequences of seizures that would leave the mature brain unaffected.[10] This finding may have special implications for the treatment of epilepsy, since the disorder so often begins in childhood. Another model with clinical implications for repetitive seizures comes from recent investigations in "kindling," where periodic electrical stimulation too mild for behavioral or electrographic effects may eventually result in spontaneously occurring seizures. Aside from the implications of repetitive electroconvulsive therapy in psychiatric disorders,[7] these observations on kindling suggest that certain types of seizure foci may be self-perpetuating. A lesion that tends to fire repeatedly may worsen simply because of the effect of frequent abnormal discharge on the cells in and about the focus.

CLINICAL EVIDENCE OF SEIZURE MECHANISMS

Heterogeneity of clinical types of epileptic seizures is the hallmark of epilepsy. The complexity of the human brain is reflected in the vari-

ety of seizure manifestations. This heterogeneity is revealed in electroencephalographic and videotape recordings of numerous seizures from patients who have only a single type of attack. Such recordings are gradually increasing our understanding of the heterogeneity of seizures, and, for the first time, allowing data-generated descriptions of the form and variety of epileptic attacks. An example of this is the absence seizure, in which heterogeneity is minimal and a basic substrate of a brief period of unresponsiveness is modified by myoclonic features, changes in postural tone, and automatisms, which vary from seizure to seizure.[6] Do the different seizure manifestations relate to different basic mechanisms of epileptic seizures? There are at least two types of seizures that relate to the different basic mechanisms of seizures: generalized and partial attacks. In other words, there is clinical evidence for at least two fundamental mechanisms of seizures. It is not certain whether these two groups may be subdivided by other factors.

Generalized Epileptic Seizures

Generalized epileptic seizures occur bilaterally and begin without a local onset. The clinical signs or symptoms are not referable to an anatomical or functional system localized to one hemisphere. Usually, consciousness is initially impaired, unless the seizure is extremely brief. Many of these epileptic seizure types are heritable, which suggests a biochemical mechanism in contrast to the partial or focal seizures often associated with a defined structural lesion of the brain. The generalized seizures include not only generalized tonic-clonic attacks, but also absence seizures,[6] photosensitive seizures,[4] and progressive myoclonus seizures.[1]

The most common type of generalized attack is generalized tonic-clonic seizures. Most lay persons think of this type of seizure when the subject of epilepsy is discussed. The loss of consciousness, tonic-clonic movements, and postictal confusion make it the most dramatic form of epilepsy. The seizures may occur at all age ranges except infancy, and are often accompanied by tongue biting and urinary incontinence.

Absence seizures are characterized by a "blank stare" accompanied by unawareness and amnesia. Most of these attacks also exhibit one or more features such as mild clonic movements, postural changes, automatisms, or autonomic phenomena such as pupillary dilatation. The onset occurs before age 16, and more than half of the seizures beginning in childhood cease or become very brief and infrequent after puberty. The ictal electroencephalogram shows generalized spike-wave discharge of 2 to 4 Hz.[6] These seizures are inherited as a Mendelian dominant; 36 per cent of siblings of affected patients will have 3/sec spike-wave discharges on the electroencephalogram.[3] The prognosis is excellent for the patients who have absence seizures as the sole type of seizure; seizure control by medication, or complete remission in 75 per cent of the cases, may be expected.[8]

Photosensitive seizures are precipitated by flickering or sudden flashing of light, usually at 15 to 20 Hz, and may be induced environmentally by intermittent exposure to sunlight or the flickering of a

television set, for example, or artificially by the stroboscope. These attacks usually occur in the form of tonic-clonic seizures, absence seizures, or myoclonic seizures. The most frequent electrical manifestation is a generalized spike-wave discharge, although high-voltage generalized polyspikes or high-voltage generalized slowing are also recorded. The majority of cases occur before age 30, with a preponderance among females, and in individuals who are otherwise neurologically normal. A prominent family history of photosensitivity and epilepsy has often been described. Although avoiding the stimulus or wearing dark glasses to reduce it can be helpful, valproic acid (Depakene) is also effective in preventing these seizures. Mechanistically, it seems likely that one or more biochemical defects may be mediated through genetic defects.

Myoclonus, the sudden involuntary jerking of a muscle or group of muscles, is observed in many diseases — some well defined and some poorly categorized. One group in the latter category is "progressive myoclonus epilepsy," a heterogeneous syndrome first described in the 1890's. The fundamental characteristics of the disorder are myoclonus and neurologic deterioration. In patients with the classic Lafora body disease, the disorder begins between the ages of 10 and 20 years, and progresses steadily and unremittingly over several years. Other progressive symptoms include ataxia, dysarthria, and emotional lability. Death occurs within 5 to 15 years after onset. Generalized tonic-clonic seizures usually occur and may be severe and difficult to control. Lafora body inclusions are seen in the brain of some patients but not of others. The cause of the disorder is unknown, but certain clues suggest a biochemical mechanism. First, many families have autosomal recessive transmission of the disease. Second, identification of a possibly accumulating product, a glucose polymer, in the Lafora body has led investigators to seek a specific enzymatic defect. Finally, it is important to recognize that other inherited diseases that are biochemically well characterized are not infrequently accompanied by the symptom of myoclonus. Valproic acid is effective for many patients with myoclonic seizures (see below).

Partial Seizures

Partial seizures occur when the attack originates from a localized area of the brain. When the abnormal neuronal discharge remains localized and involves only one hemisphere, consciousness is usually spared and the attack is termed "simple partial." An example of such an attack is the "focal motor" seizure, with jerking of a limb for several seconds during which the patient is conscious and alert. If, however, the abnormal discharge spreads to involve the opposite hemisphere, consciousness is altered and the ability to respond appropriately is impaired. The attack is then termed "complex partial" and may be associated with integrated complex behavior known as automatisms. A typical example of a complex partial seizure is the paroxysmal onset of a bad taste, followed by unresponsiveness, fumbling of the hands, and smacking of the lips; after 60 seconds, the patient slowly becomes reoriented and in 3 minutes is back to normal

except for some mild lethargy. Either simple partial or complex partial seizures may progress to generalized tonic-clonic seizures.

Several types of lesions may cause partial seizures. Traumatic lesions can cause seizures appropriate to the area of damage. Hypoxia usually causes seizures that arise from the sensitive cells of the temporal lobe. Tumors cause seizures in rough proportion to their proximity to the cortex and partly in relation to their histologic type. A hypothalamic or parietal glioma is much less likely to be associated with seizures than a frontal or temporal glioma; a slowly growing astrocytoma is more likely to cause seizures than a rapidly growing glioblastoma. In many cases of partial seizures, a structural lesion is not identifiable, even though it may be possible to define a focus by clinical and electroencephalographic criteria.

The evidence of localization of partial seizures comes from several sources. The clinical onset itself may be the best clue, as in the above example of a simple partial seizure, in which the lesion is usually localized in the contralateral motor cortex. Likewise, an olfactory aura (which is a simple partial seizure) may localize the lesion to the uncal region; if the attack continues with subsequent loss of consciousness, one may still infer that it started in the uncal region. Although some complex partial seizures may begin with focal features characteristic of a specific region of the brain, others may begin simply with loss of consciousness, making localization more difficult. If the diagnosis of complex partial seizures is secure, then it is most likely that the temporal lobe is the beginning site of the abnormal discharge. Unfortunately, such statistical likelihood is not very useful, as some complex partial seizures begin in other parts of the brain, such as the frontal lobes.

In most cases in which localization is clinically prominent, the interictal electroencephalogram confirms the area of abnormal discharge. In complex partial seizures, where such localization may be inapparent clinically, the electroencephalogram may be critical in localizing the abnormal discharge. If a temporal lobe is identified as the origin, surgical extirpation may be appropriate for medically intractable complex partial seizures.

MODERN USE OF ANTIEPILEPTIC DRUGS

Proper therapy for seizure disorders is highly dependent on the correct diagnosis; these two concepts will, therefore, be discussed together. It is important to recognize that epileptic patients require both an etiologic and a seizure diagnosis. The former refers to the causative agent or lesion that is fundamentally responsible for the seizures; this may be an infection, a tumor, an injury, or any of a large group of other causative factors. A review of the proper neurologic evaluation of the etiologic diagnosis is beyond the scope of this article, but the determination is critically significant. Although an etiologic diagnosis is often not established, all etiologically undiagnosed epileptic patients

should undergo periodic review to assure that such a diagnosis remains unachievable. This is especially true for patients with partial seizures.

The seizure diagnosis can almost always be established, usually from the history alone. The importance of retrieving the necessary information for proper classification of the patient's seizures cannot be overemphasized, as subsequent therapy depends on these data.

The proper seizure diagnosis determines the choice of antiepileptic medication, but certain pharmacologic principles apply to the most effective use of these drugs. The pharmacologic properties of the six most useful antiepileptic drugs are shown in Table 1.[5]

The major pharmacologic principles for oral drugs relate to drug absorption, distribution, and elimination. Drug absorption depends on the ability of the gastrointestinal tract to facilitate entrance of the ingested drug into the blood (assuming patient compliance), and is a function of the properties of the drug and its interaction with the cell membranes of this tract. All antiepileptic drugs are of small molecular weight and also cross lipid membranes with relative ease, allowing almost total absorption of the drug in most cases. Exceptionally, a specific absorption defect in some patients may interfere with the bioavailability of the drug. Another exception is the rate of absorption, which may vary with different drug preparations. Some recent problems have arisen with phenytoin, for example, in which single-day dosage of a rapidly absorbed preparation caused toxicity. The rate of absorption is also highly dependent on drug intake in relation to meals. Drugs taken when the stomach is empty may be absorbed much more rapidly than those taken directly after a meal. This observation can be very useful, especially for rapidly absorbed drugs or drugs with a short half-life (see below) in which it is desirable to slow absorption and avoid peaks of serum drug concentrations with possible transient toxicity.

Antiepileptic drugs, whose lipid solubility is generally high, are distributed to all body tissues in various proportions. The brain concentration is, in most cases, equal to or greater than that of other body tissues. More importantly, the brain and blood concentrations of antiepileptic drugs are apparently proportional; the blood concentrations can therefore be used as an important guide to therapy.

The most important pharmacologic principle to be understood is the elimination half-life. Although a drug may be eliminated by metabolism, storage, or excretion, the major clinical concern is with the rate of disappearance of the drug rather than the specific route of disappearance. This rate is usually expressed as the half-life of the drug and refers to the time required to remove half of the active drug from the body. The half-lives have been determined for all antiepileptic drugs (and to a large extent, their active metabolites as well) and are useful in therapy as a guide to the following:

1. *Frequency of administration.* Drugs with longer half-lives, such as phenytoin (Dilantin) and phenobarbital, can be administered once or twice daily without large fluctuations in their concentrations

Table 1. *Pharmacologic Properties of Six Antiepileptic Drugs**

DRUG	DOSAGE (mg/day)	EXPECTED BLOOD LEVEL		TIME TO REACH STEADY-STATE BLOOD LEVELS (days)	SERUM HALF-LIFE (h)	EFFECTIVE BLOOD LEVEL (μg/ml)	TOXIC BLOOD LEVEL (μg/ml)	PROTEIN BOUND (%)
		Average (μg/ml)	Range (μg/ml)					
Phenytoin (Dilantin)	300	10	5–20	5–10	24 ± 12	>10	>20	90
Phenobarbital (Luminal)	120	20	10–30	14–21	96 ± 12	>15	>40	40–50
Primidone (Mysoline)	750	8	5–15	4–7	12 ± 6	>5	>12	0–50
Phenobarbital	Derived	24	5–32	14–21	–	–	–	–
Carbamazepine (Tegretol)	1200	6	3–12	2–4	12 ± 3	>4	>8	70
Valproic acid (Depakene)	1500	50	40–70	2–4	12 ± 6	>50	>100	90
Ethosuximide (Zarontin)	1000	60	40–100	5–8	30 ± 6	>40	>100	0

**From* Penry, J. K., and Newmark, M. E.: The use of antiepileptic drugs. Ann. Intern. Med., *90*:207–218, 1979. Reproduced with permission.

in the blood. Drugs such as carbamazepine (Tegretol) and valproic acid have much shorter half-lives and may require more frequent administration.

2. *Time to reach steady state.* Drugs with long half-lives may require many days to reach steady state at a new dose level. The time needed to reach steady state is approximately six times the half-life of the drug. This means that drugs such as phenobarbital and phenytoin may require 5 to 10 days or more to reach steady state, but that drugs such as carbamazepine and valproic acid will reach steady state in 2 to 4 days.

3. *Time to effectively eliminate the drug.* If a drug is suddenly discontinued, it will disappear at a rate related to its half-life in the same way it reaches steady state; that is, a drug with a long half-life will take longer to disappear than one with a short half-life.

It is important to note that these principles are independent of dose or dose change. This assumption is inherent in first order pharmacokinetics, but it may not be accurate at high dosage levels and with certain drugs that have "saturation kinetics." To avoid clinical difficulty, it should be assumed that the half-life may be much longer for phenytoin and other drugs with a similar half-life when the dosage level is at the upper end of the therapeutic range. Changes in dosage should be accomplished more slowly in this range.

There are other important pharmacologic principles not directly related to the pharmacokinetics described above. For example, several antiepileptic drugs have active metabolites, which may have much longer half-lives than the parent compounds. Some of these are primidone (Mysoline), which is rapidly converted to phenobarbital (and phenylethylmalonamide); methsuximide (Celontin), which is rapidly converted to desmethylmethsuximide; and mephenytoin (Mesantoin), which is converted to Nirvanol. Proper evaluation of the antiepileptic effect of these drugs must include consideration of the active metabolite of each.

Another pharmacologic principle of importance relates to the use of single drugs and problems of polypharmacy. The tendency to utilize more drugs than needed to obtain maximal seizure control has often subjected patients to unnecessary toxicity. Recent studies suggest that single drug therapy may be superior to multiple drug regimens in mild to moderately affected patients, thus strongly reinforcing the recommendation of trying single drugs first.

Whenever possible, the sedative medications that interfere with behavioral and functional aspects in both children and adults should be avoided. This is especially true for the benzodiazepines and the barbiturates; there are often good alternatives to these drugs that do not have their toxic side effects.

Proper therapy relies on an understanding of the above principles and the correct seizure diagnosis. The selection of an appropriate antiepileptic drug depends on whether the patient has generalized or partial seizures.

Generalized tonic-clonic seizures are usually the easiest to treat. They respond to phenytoin or carbamazepine. In resistant cases, both

should be used together. If control is not possible with these two drugs, it may be necessary to resort to a barbiturate or desoxybarbiturate.

The partial seizures respond to the same drugs used for generalized seizures, a coincidence that may reflect the secondary origin of most generalized tonic-clonic attacks. Phenytoin and carbamazepine are effective for partial seizures, and neither has a prominent sedative effect. In intractable cases, the two drugs can be used together; the use of barbiturates should be reserved for cases not responsive to this combination.

Two drugs recently introduced in the United States and of major importance to the therapy of patients with epilepsy deserve special discussion. The first of these is carbamazepine. It is a tricyclic compound closely related to currently used antidepressants. The drug was developed in the 1950's and was marketed outside the United States in 1962; it was approved here in 1968 for the treatment of trigeminal neuralgia (tic doloreux) and in 1974 for epilepsy. Deaths from bone marrow depression during the early years of its use caused considerable alarm and greatly retarded its prescription. This problem is quite rare and does not appear to differ from the idiosyncratic reactions of other drugs. The drug is efficacious for partial and generalized tonic-clonic seizures in both children and adults. It is not effective for absence or atonic seizures. It is well tolerated if given in divided doses after meals and at bedtime. The most common complaint of toxicity is diplopia, lasting 30 to 60 minutes and occurring shortly after a dose; rearrangement of administration can usually negate this problem without lowering the total daily dose. A morning, fasting concentration in the blood of 5.5 to 7.5 μg per ml usually indicates maximal efficacy without toxicity. Pediatricians find carbamazepine especially valuable because it does not have the sedative and behavioral side effects of the barbiturates and benzodiazepines, and it does not coarsen the face, cause hirsutism, or induce gum hypertrophy, as does phenytoin. Whether the positive psychotropic effects of carbamazepine are related to a primary effect or are the result of decreased doses of other, more toxic compounds, remains unproved; in any case, many patients have greatly benefitted from its use.

If the sole type of seizure is absence attacks, the patient should be treated with ethosuximide (Zarontin) or valproic acid, or both in resistant cases (see below). Another generalized type of seizure, infantile spasms, is usually characterized by single, repetitive jerks of the arms or head or both and is associated with mental retardation in most cases. Ninety per cent of first attacks occur before the age of one year. Therapy is ineffective for the retardation, but the seizures sometimes respond to courses of ACTH or corticosteroids. Other drugs less likely to be effective are nitrazepam (not available in the United States), clonazepam (Clonopin), and valproic acid.

Atonic seizures should be suspected if the patient has a very abrupt loss of tone many times per day, with frequent severe falls and with the head dropping forward suddenly. The attacks are often seen in patients who have other types of generalized seizures and are par-

ticularly difficult to treat. Valproic acid may be the best drug for these patients (see below).

Approved for use in the United States in 1978, valproic acid was noted to have antiepileptic properties in the early 1960's. It is effective for absence and myoclonic seizures. Its usefulness for generalized tonic-clonic seizures remains promising but unproved. The drug may be used concurrently with ethosuximide for resistant absence seizures; unlike ethosuximide, it has a short half-life and should be given in divided doses throughout the day. Valproic acid has some toxic side effects not typical of antiepileptic drugs: temporary hair loss, hyperphagia, and tremor at high doses; these are dose related and reversible. Tests for liver dysfunction, such as SGOT, are indicated, particularly early in the course of treatment, because hepatic failure is the only well documented severe side effect; it is very rare. The drug may have a mechanism of action that will increase our understanding of epileptic processes; it appears to inhibit the enzyme that degrades GABA, an inhibitory transmitter, perhaps leading to an accumulation of this compound and to decreased neuronal excitability. Regardless of its mode of action, it is a welcome addition to the antiepileptic armamentarium.

CONCLUSIONS

Many possible fundamental causes of epileptic seizures have been suggested. None of these mechanisms, however, gives us complete understanding of clinical seizures. On the contrary, we have remarkably little understanding of many of the basic epileptic processes. Despite these limitations, empirical information on the clinical epilepsies continues to expand and to be increasingly valuable diagnostically and therapeutically. The most important diagnostic information is the clinical type of seizure, and the ictal and interictal electroencephalographic abnormalities. The most significant therapeutic considerations are proper choice of medication, depending on the seizure diagnosis, and sound application of pharmacologic principles to obtain the maximum effect of medical treatment.

REFERENCES

1. Charlton, M. H., ed.: Myoclonic Seizures. Amsterdam, Excerpta Medica, 1975, 167 pp.
2. Gastaut, H.: Clinical and electroencephalographical classification of epileptic seizures. Epilepsia, *11*:102–113, 1970.
3. Metrakos, K., and Metrakos, J. D.: Is the centrencephalic EEG inherited as a dominant? Electroencephalogr. Clin. Neurophysiol., *13*:289, 1961.
4. Newmark, M. E., and Penry, J. K.: Photosensitivity and Epilepsy: A Review. New York, Raven Press, 1979.
5. Penry, J. K., and Newmark, M. E.: The use of antiepileptic drugs. Ann. Intern. Med., *90*:207–218, 1979.
6. Penry, J. K., Porter, R. J., and Dreifuss, F. E.: Simultaneous recording of absence seizures with video tape and electroencephalography. A study of 374 seizures in 48 patients. Brain, *98*:427–440, 1975.

7. Pinel, J. P. J., and Van Oot, P. H.: Generality of the kindling phenomenon: Some clinical implications. *In* Wada, J. A., ed.: Kindling. New York, Raven Press, 1976, pp. 155–171.
8. Sato, S., Dreifuss, F. E., and Penry, J. K.: Prognostic factors in absence seizures. Neurology (Minneap.), 26:788–796, 1976.
9. Ward, A. A., Jr.: Theoretical basis for surgical therapy of epilepsy. *In* Purpura, D. P., Penry, J. K., and Walter, R. D., eds.: Neurosurgical Management of the Epilepsies, Advances in Neurology, Vol. 8. New York, Raven Press, 1975, pp. 23–35.
10. Wasterlain, C. G., and Plum, F.: Vulnerability of developing rat brain to electroconvulsive seizures. Arch. Neurol., 29:38–45, 1973.
11. Woodbury, D. M.: Convulsant drugs: Mechanisms of action. *In* Glaser, G. H., Penry, J. K., and Woodbury, D. M., eds.: Antiepileptic Drugs: Mechanisms of Action, New York, Raven Press (in press).
12. Wyler, A. R., Burchiel, K. J., and Ward, A. A., Jr.: Chronic epileptic foci in monkeys: Correlation between seizure frequency and proportion of pacemaker epileptic neurons. Epilepsia, *19*:475–483, 1978.

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The Unresponsive Patient

Diagnosis and Early Management

Bruce Sigsbee, M.D., and Fred Plum, M.D.***

An altered state of consciousness represents a disruption of the structural, metabolic, or psychological integrity of the brain that can range from barely detectable changes in clarity of thought to the absence of clinically detectable brain function. This communication deals primarily with physiologic impairments of consciousness. Admittedly, a potentially bewildering list of potential causes of altered levels of consciousness confronts the physician. Nevertheless, when faced with the clinical problem, the initial steps in diagnosis and management can be guided in a logical manner by the information available.

The history is a major source of information; but it is often unavailable or misleading. At these times the physical findings determine the importance and order of diagnostic and therapeutic interventions. Described below is an ordered approach to the early diagnosis and management of the unresponsive patient based on the physical examination (Table 1).

Definitions

Consciousness depends on two types of function, arousal and cognitive. *Clouding of consciousness* is a state in which both functions are impaired. It may be accompanied by altered affect. Patients with incipient clouding are less alert, are distractable, and are often irritable, anxious, or excitable. Further cerebral impairment induces an *acute or subacute confusional state*. Disorders of arousal are prominent. Patients in such states are drowsy and distractable. They often fall asleep during the examination. Disorientation appears, first to time, then to place, and rarely to person. Apathy in some patients may delay recognition of the confused state. Clouding of consciousness re-

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Table 1. *Approach to the Unresponsive Patient*

Initial contact:	Assure delivery of blood, oxygen, and glucose to the brain.
History:	Search for prior illness – particularly psychiatric and medical – and define the onset, evolution, and characteristics of the altered state of consciousness.
Examination:	Evaluate the level of consciousness, the pattern and depth of respiration, the pupils, the oculovestibular reflexes and the skeletal muscle motor responses.
Diagnosis:	On the basis of available information, consider supratentorial mass lesions, subtentorial structural lesions, multifocal versus diffuse brain dysfunction, and psychogenic causes.
Management:	Proceed with further tests or treatment based on the tentative diagnosis.

sults from widespread multifocal structural lesions or metabolic disorders.

Delirium is a state characterized by agitation, vivid hallucinations, fear, gross cognitive impairment, and autonomic overactivity (diaphoresis, tachycardia, diarrhea). It is distinguished from other forms of clouding of consciousness by a profound impairment of psychological contact with the environment despite the aroused, agitated appearance.[1, 24] The usual causes of delirium are alcohol-sedative-hypnotic withdrawal, encephalitis, and toxic psychoses, such as those caused by amphetamines, anticholinergics, and phencyclidine.

Stupor is a sleep-like state from which the patient can be aroused only by vigorous and persistent stimulation.

Coma is a sleep-like state from which the subject cannot be aroused.

INITIAL CONTACT WITH THE PATIENT

If the cause of coma is unknown, one must take immediate steps to prevent further injury to the central nervous system. Based on observations in man and in animal models,[7, 28, 36] the priorities for preventing further neuronal damage are, in order, (1) maintenance of cerebral blood flow (perfusion pressure) by correction of impaired heart rhythm and blood pressure; (2) attention to oxygenation by provision of an adequate airway and respiratory effort; and (3) provision of an adequate blood glucose level (Table 2). Glucose should be administered only *after* a blood sample is drawn, so as not to lose evidence of hypoglycemia.

A brief examination will determine if specific diagnostic and therapeutic maneuvers may be harmful. In particular, head trauma may be associated with cervical spine injury. In this circumstance, manipulation of the neck during intubation could damage the spinal cord. Puncture of large central vessels, for example puncture of the subclavian vein for placement of a central venous line, or puncture of the femoral artery for blood gas determinations, should not be performed in patients with evidence of a bleeding diathesis.

Table 2. *Initial Contact with the Patient: Steps to Assure Adequate Supply of Substrates for Oxidative Metabolism in Order of Importance*

1. Maintain perfusion pressure:
Check heart rate and rhythm
Check blood pressure
Treat accordingly
2. Oxygenate:
Check airway
Check respiratory rate
Intubate and support respiration if indicated
Draw blood for blood gas determinations if oxygenation appears adequate
Treat with low flow nasal oxygen (5 liters per minute)
3. Provide glucose:
Draw blood for glucose determination
Give glucose (50 cc dextrose 50% in water)
Repeat administration if patient is hypoglycemic

NEUROLOGIC EXAMINATION OF THE PATIENT IN COMA

When a patient is in coma, the absence of volition limits the neurologic examination to evaluation of reflex and homeostatic mechanisms. A knowledge of the anatomy and physiology of forebrain and brainstem permits discrimination between supratentorial mass lesions, subtentorial structural lesions, diffuse or multifocal central nervous system disease, and psychogenic unresponsiveness. The basic observations are the level of consciousness, respiration, pupillary function, reflex eye movements, and motor responses. Plum and Posner[33] provide a detailed discussion of the pathophysiology and differential diagnosis of stupor and coma.

Consciousness

Arousal depends on structures within the brainstem, and cognition on the functions of the cerebral hemispheres. Arousal is mediated by the reticular system, a diffuse collection of gray matter and nuclei with indistinct boundaries lying within the brainstem tegmentum. Moruzzi and Magoun[29] demonstrated that lesions limited to the reticular formation with preservation of the ascending primary sensory pathways resulted in coma. They coined the term ascending reticular activating system (ARAS) to describe the functional role of the reticular formation. In animals bilateral damage to the reticular formation in the rostral third of the pons, the medulla, or the dorsal hypothalamus will result in stupor or coma. Clinical-pathological observations indicate that the same anatomic limits of the reticular formation apply to man.

Cognition consists of the sum of complex memory, analytic, interpretive, emotional, and language functions. These cannot be tested in the comatose patient, but focal defects in cognitive function, e.g. aphasia, may precede coma caused by a supratentorial mass lesion.

The early stages of diffuse or multifocal central nervous system disease, the confusional states, produce recognizable changes in cognitive function.

Altered consciousness — lethargy, stupor, or coma — implies dysfunction either of both cerebral hemispheres or of the brainstem rostral to the mid pons or both. An important possible exception is the temporary marked depression in the level of consciousness that can occur with acute extensive damage to the dominant hemisphere.[2]

Respiration

Respiration is regulated by both a brainstem mechanism that subserve metabolic requirements and forebrain influences that subserve behavior.[4] Altered respiratory patterns occur with lesions at all levels of the central nervous system.

Normal subjects will resume breathing within 10 seconds after lowering the arterial carbon dioxide by hyperventilation. In subjects with diffuse disease of the forebrain caused by either structural or metabolic injury, *post-hyperventilation apnea* can last up to 30 seconds or more.

Periodic or *Cheyne-Stokes respiration* is an oscillating respiratory pattern that alternates between hyperventilation and hypoventilation or apnea. The common cause is disease of the central nervous system, alone or together with cardiac disorders which prolong the circulation time. The neurologic causes range from dementing degenerative diseases to early transtentorial herniation. Anatomically, periodic respiration is associated with bilateral hemispheric or diencephalic insults.

Central neurogenic hyperventilation is a sustained alveolar hyperventilation associated with destructive lesions of the rostral pontine and mesencephalic reticular formation. Pure central neurogenic hyperventilation is rare. Most patients with hypocapnia and an increased respiratory rate have pulmonary disease, either overt or reflected by a depressed arterial Po_2.[13] Such relative hypocapnia and hypoxia can result from neurogenic pulmonary edema.[8] It is also commonly associated with many severe illnesses. According to Leigh and Shaw, an increased regularity of respiration rather than an increased rate correlates with lesions of the central brainstem.[23]

Direct injury to the respiratory control mechanisms in the caudal pons and medulla produces several abnormal respiratory patterns. *Apneusis* is a protracted maintenance of full inspiration or expiration. *Ataxic respirations* are irregular in rate and magnitude. Respirations may come in *clusters* with intervening apnea or the respiratory effort itself may be jerky and *ratchet-like*. These respiratory patterns generally fade into a terminal apnea.

Pupils

Pupillary size reflects a balance between sympathetic (mydriasis) and parasympathetic (miosis) tone. The pupillary light reflex is mediated solely through the parasympathetic system; the afferent path-

way is the optic nerve and tract and the efferent pathway is the oculomotor nerve.

Lesions that interrupt the central or peripheral sympathetic nerves will result in ipsilateral miosis and, usually, ptosis and anhydrosis (Horner's syndrome). Specific causes of Horner's syndrome are lesions of the hypothalamus, pontine tegmentum, lateral medulla, ventrolateral spinal cord, and peripheral sympathetic nerves. Tectal and pretectal lesions damage the afferent loop of the pupillary light reflex but leave constriction to accommodation and the sympathetic innervation intact. The pupils are midposition to large and irregular, exhibiting hippus characterized by spontaneous constriction and dilatation. Lesions of the midbrain destroy both the sympathetic and parasympathetic systems; the pupils are midposition, irregular, and fixed. Pontine hemorrhage is associated with pin-point but reactive pupils.

The state of the pupil also helps to discriminate between mass lesions and diffuse central nervous system disease (Fig. 1). In general, during toxic and metabolic coma, the pupillary light reflex, though typically sluggish, is preserved until the patient is terminal. In contrast, the pupillary light reflex is lost early in transtentorial herniation caused by mass lesions. Important exceptions may give rise to diagnos-

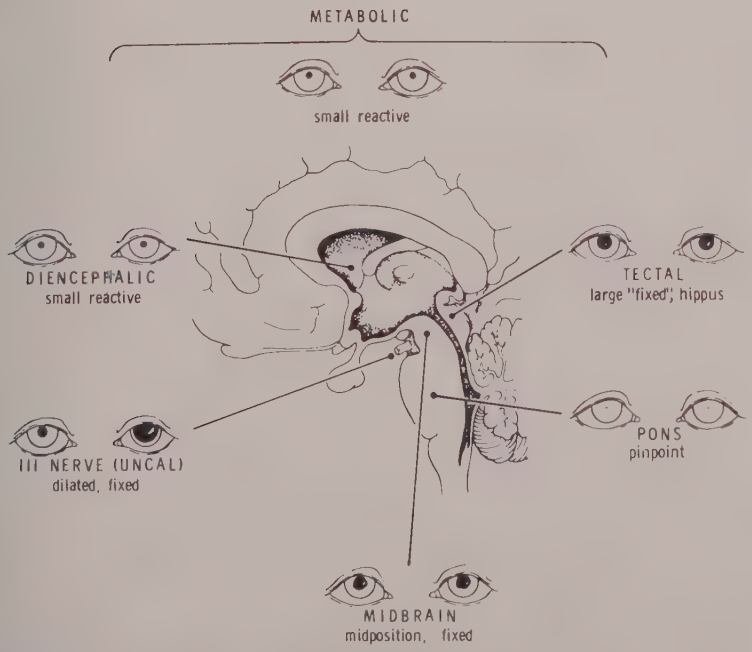

Figure 1. Pupils in the unresponsive patient. (From Plum and Posner, Stupor and Coma, 1972, by permission of the publisher, F. A. Davis.)

tic uncertainty. Overwhelming anoxia or ischemia may be associated with pupillary dilatation. Atropine and scopolamine produce dilated unreactive pupils. Glutethimide causes midposition to large irregular pupils that are unreactive to light. Opiates produce pin-point pupils. Near-fatal barbiturate intoxication can fix the pupils.

Only after examination with a bright light and observation with magnification can the pupillary light reflex be regarded as absent.

Ocular Movements

The oculomotor system extends from the forebrain to the mid pons. Testing of both voluntary and reflex ocular movements provides an important source of information.

The supranuclear control of gaze originates in frontal and occipital "gaze centers." The occipital region subserves slow movements of pursuit and the frontal regions subserve saccadic movements. The fibers responsible for conjugate lateral gaze descend to the contralateral abducens nucleus via separate pathways (Fig. 2*A*). An internuclear pathway extends from the contralateral abducens nucleus to the ipsilateral oculomotor nucleus via the medial longitudinal fasciculus. Horizontal gaze is thus mediated by the cerebral hemisphere, the contralateral abducens nucleus and the ipsilateral oculomotor nucleus.

The vestibular nuclei tonically and symmetrically stimulate the oculomotor system (Fig. 2*B*). Vestibular tone is in turn altered by the

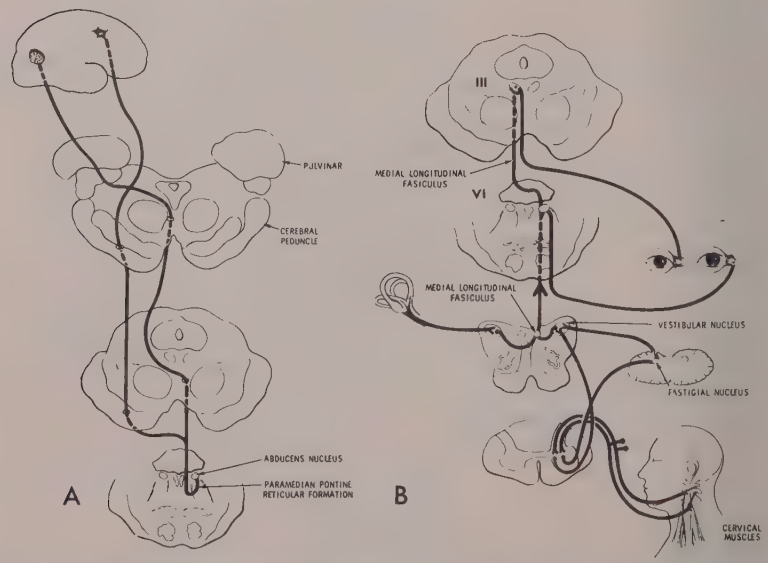

Figure 2. *A.* Supranuclear control of Horizontal Gaze. *B.* Brainstem pathways for Horizontal Gaze. (From Plum and Posner, Stupor and Coma, 1972, by permission of the publisher, F. A. Davis.)

semicircular canals and proprioceptive afferents. If this symmetry is disrupted, the eyes will tend to deviate toward the nucleus with the relative decrease in tone. Clinically, this reflex alteration in vestibular tone is elicited by turning the head, the oculocephalic reflex, or by cooling or warming the semicircular canals, the oculovestibular reflex.

The oculocephalic reflex is performed by rolling the head from side to side. Vestibular tone is increased on the side to which the head is turned, thus the eyes tend to deviate in the opposite direction.

The oculovestibular reflex induces an even greater asymmetry in vestibular tone. After examination of the auditory canal and tympanic membrane, the head is elevated to 30 degrees above the horizontal. In the awake patient, cold water or a small amount of ice water (1 to 5 ml) is slowly injected into the auditory canal (caloric test) via a tube placed near the tympanic membrane. In the unconscious patient, ice water is slowly and gently infused until deviation occurs or to a maximum of 200 ml. Cold water decreases the vestibular tone on the infused side; with preserved brainstem function the eyes will deviate toward the side injected.

If supranuclear innervation is intact, jerky, irregular saccadic movements will oppose the tonic deviation. If brainstem reflexes are intact but supranuclear input is lost, the eyes will deviate tonically. If pontine structures are damaged, the eyes will not deviate. If the midbrain is damaged, leaving the pons intact, ipsilateral abduction is observed.

At rest, abnormalities of eye position are conjugate or dysconjugate. Conjugate deviation occurs with sudden unilateral loss of supranuclear input into the horizontal gaze center of the brainstem. The eyes will then deviate to the side of the hemispheric lesion. Oculovestibular reflex testing can drive the eyes in the opposite direction. Hemispheric irritative lesions such as some hemorrhages or epileptic discharges will drive the eyes to the side opposite to the involved hemisphere. Unilateral pontine tegmental lesions that damage the pontine gaze center result in the conjugate deviation of the eyes contralateral to the side of lesion; caloric testing in this case will not drive the eyes past the midline.

Resting deviation of the eyes below the horizontal meridian denotes brainstem dysfunction, most often from compression of the brainstem tectum. More extensive brainstem dysfunction from structural or rarely metabolic disease can also cause downward deviation.

Dysconjugate horizontal eye position at rest represents damage to the nuclear or internuclear pathway. Of note, depression of the level of consciousness by either metabolic or structural lesions may often uncover a latent vertical or horizontal strabismus. Therefore, dysconjugate eye position is a fully reliable sign only in the awake patient.

Persistent skew deviation of the eyes, one up and the other down, in an awake patient suggests structural disease of the brainstem.[20] Skew deviation rarely is observed in metabolic disorders, notably drug overdoses.

Roving eye movements are slow, conjugate, and usually horizon-

tal, though vertical movements do occur. The presence of these movements requires intact brainstem and probably diencephalic function with loss of more rostral hemispheric function. The movements cannot be duplicated voluntarily.

Motor Function

In the stuporous or comatose patient, motor responses to noxious stimuli can be appropriate, inappropriate, or absent. *Appropriate* responses, e.g. withdrawal from or resistance to the noxious stimulus, confirm that sensory and corticospinal pathways are intact. *Inappropriate* motor responses are stereotyped, the pattern depending on the level of the lesion. *Decorticate rigidity* consists of flexion of the arms, wrist, and fingers, and extension and internal rotation of the legs. It occurs with dysfunction or lesions of the cerebral hemispheres. *Decerebrate (extensor) rigidity* consists of extension and internal rotation of both the arms and legs. It usually emerges in man after at least partial isolation of the midbrain-pontine structures from rostral input. Decerebrate posturing of the upper extremities and flexion or flaccid weakness of the lower extremities denotes extensive brainstem damage, extending to the mid-pons. Absent motor responses reflects damage or depression extending to motor centers in the lower brainstem.

MASS LESIONS CAUSING COMA

Structural lesions vary in their clinical presentation according to their size, rate of development, number, position in the brain, and the degree of intracranial shift they cause. Small, multiple and disseminated structural lesions in sum can mimic the clinical signs of metabolic brain disease, they are considered together with metabolic brain disease in a later section. Large structural lesions that cause coma by mass effect and herniation cause a limited number of recognizable syndromes.

Any increase in one of the major constituents of the intracranial contents — blood, cerebrospinal fluid, or tissue — will eventually increase the intracranial pressure. Despite the rigidity of the skull, an increase in the intracranial pressure alone will not cause herniation as demonstrated experimentally by increased cerebrospinal fluid pressure after infusion of saline[37] and spontaneously by patients with pseudotumor cerebri. Rather, tissue shifts require a pressure gradient from one point within the skull to another.

An expanding mass lesion adds to its mass effect not only by adding to its substance, e.g., growth of a tumor, but also by inducing changes in the adjacent parenchyma, e.g., glial proliferation, edema, and vasodilatation caused by failure of autoregulation. In the unyielding skull, the expanding cerebral structures shift first across the midline then down through the tentorial notch or foramen magnum. Successive regions are compressed, injured, and reactively swollen.

Eventually, obstruction of cerebrospinal fluid and venous drainage

augments the mass effect. Blood vessels lose their capacity for autoregulation, adding an increased blood volume to the already crowded intracranial contents. The mass effect of an acute lesion is generally greater because of the greater parenchymous reaction. The clinical effect is production of signs of spreading zones of dysfunction, best exemplified by transtentorial herniation due to supratentorial mass lesions.

Supratentorial Mass Lesions

The identification of sequential anatomic deterioration or a stage in the sequence is the clue to recognition of a supratentorial mass lesion causing coma (Table 3). Initially, intraparenchymal mass lesions cause focal hemispheric dysfunction, such as weakness, sensory defects, visual field defects, focal seizures, aphasia or focal cognitive defects. With increasing mass effect, central hemispheric structures are compressed and shifted across the midline. This compromise of the diencephalon produces the first recognizable stage in transtentorial herniation. In contrast, extraparenchymal mass lesions, such as subdural hematomas, often cause few or no focal signs and produce diencephalic dysfunction as the earliest evidence of neurological dysfunction.

The early manifestations of diencephalic compression are inattention and difficulty concentrating. Apathy or agitation are inconsistently present. Subsequently, drowsiness, stupor and coma supervene. Sighs and yawns may be observed early, and are later replaced by Cheyne-Stokes respirations. The pupils are small and briskly reactive. Either resting or roving eye movements occur. Once coma occurs, oculocephalic and oculovestibular reflexes are brisk and full. Bilateral corticospinal tract dysfunction is present early. If the lesion is intraparenchymal, the early contralateral hemiparesis will be followed by ipsilateral paratonia, hyperreflexia, grasp reflexes, and extensor plantar responses. Eventually decorticate posturing appears, typically at first contralateral to the mass lesion.

With further shift of diencephalic structures through the tentorial

Table 3. *Clues to Supratentorial Mass Lesions as a Cause of Coma*

Focal hemisphere lesion: hemiparesis, hemisensory defect, homonymous hemianopia, focal cognitive defect, or aphasia.
Lethargy or stupor without focal brainstem or cerebellar signs
Gradual depression in the level of consciousness (except trauma)
Depressed level of consciousness more prominent than confusion
Third nerve palsy precedes coma
Sequential rostral to caudal deterioration of brain-stem function

notch, the front of dysfunction advances down the brainstem. Hyperventilation replaces the periodic respirations. The pupils dilate to midposition (3 to 5 mm) and are fixed and often irregular. The oculovestibular reflex is difficult to elicit. The adductor portion of the reflex is lost; the eyes deviate laterally, not medially. Motor responses progress from decorticate to decerebrate rigidity. At least in adults, almost no patient with a fully developed midbrain syndrome from transtentorial herniation recovers normal function. Most die. The later stages in transtentorial herniation are detailed elsewhere.[33]

Mass lesions that lie within the temporal lobe, or extraparenchymal masses that lie superficial to the temporal lobe, e.g., epidural hematomas, can directly compress the rostral midbrain without first producing diencephalic compression. This form of transtentorial herniation is termed *uncal herniation;* the uncus crowds over the tentorial margin to squeeze adjacent structures.

The most consistent sign of the early stage of uncal herniation is unilateral pupillary dilatation with a sluggish response to light. Since the diencephalon is not necessarily compressed, the state of alertness at this stage varies between near normal to stupor or coma. The respiratory pattern, eye movements, and oculovestibular reflexes are normal. Motor changes reflect the location of the mass lesion.

Once the pupil fully dilates, a complete third cranial nerve palsy and coma soon follow. As the opposite cerebral peduncle is compressed, ipsilateral hemiplegia often develops. Shortly, bilateral motor signs evolve, succeeded by decerebrate posturing. Thenceforth, the uncal syndrome is indistinguishable from the central herniation syndrome.

The danger of the uncal syndrome is that herniation and brain death proceed rapidly once this early stage is passed. The warning offered by the diencephalic stage of central herniation is absent. Delays in the institution of effective treatment may lead to irreversible or fatal brain damage.

Specific Supratentorial Mass Lesions Causing Coma

The recognition that the coma is caused by a supratentorial mass lesion is generally straightforward. The differential includes the broad categories of vascular, neoplastic or inflammatory lesions. Focal hemispheric deficits usually bring the patient to the physician prior to depression in the level of consciousness. The evolution of the mass effect is gradual rather than precipitous. However, because of a rapid evolution and/or lack of focal signs, head trauma and extraparenchymal mass lesions present diagnostic problems.

Nonpenetrating *head trauma* produces a variety of extracranial and intracranial lesions. Brief, immediate loss of consciousness following trauma is termed concussion. The coma is brief and respiration and brainstem reflexes are preserved. Caloric testing reveals nystagmus. Confusion persists for a variable period of time following awakening and some degree of amnesia is often present. The clinical features are nonspecific, being similar to those of the metabolic

encephalopathies and the postictal state. The diagnosis is suggested by the history or evidence of cranial trauma, such as scalp laceration, hematoma, and edema; dissecting ecchymosis resulting from temporal bone fracture over the mastoid area (Battle's sign) or bilateral periorbital ecchymosis resulting from a basilar skull fracture; and cerebrospinal fluid leakage. Prolonged coma or the evolution of new neurologic signs following stabilization or improvement is ominous and may indicate impending herniation due to an extradural or subdural hematoma; cerebral hemorrhage; and cerebral edema, contusion, or ischemia.

Epidural hematomas are an important cause of herniation and death following head trauma. The head trauma may be relatively mild, not immediately causing an alteration in consciousness. Epidural hematomas arise from injury to the meningeal arteries or veins or dural sinuses with skull fracture or stripping of the dura from the calvarium. Almost three-fourths of epidural hematomas occur in the temporoparietal region, the remainder arise in a roughly even distribution in other extradural sites.[17] In nearly 50 per cent, the head trauma is not sufficiently severe to cause loss of consciousness. Only 15 per cent of patients have the classic "lucid interval," characterized by awakening then deteriorating. In awake patients, the initial complaint is of increasing headache. Increased restlessness or irritability signals deterioration in the stuporous patient. An expanding hematoma lying in the temporoparietal region will then produce uncal herniation. Once initiated, uncal herniation evolves rapidly. In the comatose and stuporous patient, pupillary dilatation is the initial sign of hematoma formation and herniation. Plain x-ray films will identify a skull fracture in about 80 per cent, and a computed tomographic (CT) scan will invariably demonstrate an acute hematoma large enough to produce symptoms. In acutely deteriorating patients, the patient should be taken directly to the operating room, foregoing additional diagnostic tests.

High speed acceleration-deceleration head injury produces acute subdural hematomas. The most frequent sites of accumulation are the anterior temporal, inferolateral frontal, and parietal regions. Uncommon sites include suboccipital, posterior fossa, and interhemispheric locations. Because of the violence of the injury, there is a high frequency of associated cortical contusions, lacerations, and intraparenchymal hemorrhages. In fact, the mass effect and prognosis are determined more by the diffuse brain injury than by the hematoma. The clinical presentation parallels that of epidural hematomas with the exception that the patients rarely awaken before deteriorating, and the mass effect typically produces central rather than uncal herniation.

Extraparenchymal mass lesions expand, displacing the brain away from the calvarium. The differential diagnosis includes hematomas, tumors, inflammatory lesions, and collections of fluid. The clinical presentation may be that of a focal hemispheric lesion but more typically patients present with evidence of bilateral hemispheric dysfunction with absent or mild asymmetries on examination.

Chronic subdural hematomas result from the gradual accumulation of blood and cellular debris in the subdural space. The process is initiated by bleeding from bridging veins. Four factors, singly or in concert, predispose to the development of chronic subdural hematomas. (1) A decrease in brain size stretches the bridging veins that run from the dura to the cerebral cortex by drawing the cortex away from the calvarium. This can result from atrophy, intravascular volume depletion, osmotic agents, and ventricular shunts. (2) Any coagulopathy, either therapeutic or intrinsic, predisposes to hematoma formation. (3) Lesions which weaken the structural integrity of the vessels themselves (e.g., arteriovenous malformations or neoplastic infiltrates) increase the likelihood of bleeding. (4) Mechanical trauma to the vessels initiates hematoma formation. At highest risk are the elderly, chronic alcoholics, and patients on anticoagulants.

The delay between head trauma and the development of symptoms averages between 4 and 6 weeks. While dense focal deficits can occur, more typically patients present with bilateral hemispheric dysfunction. The onset is commonly insidious with clouding of consciousness blending into the early central transtentorial herniation syndrome. Approximately 80 per cent of patients complain of headache or skull tenderness to percussion. Mild to moderate focal abnormalities or asymmetries can be elicited on careful examination in about 75 per cent of patients. There is a tendency for the clinical status to fluctuate from day to day or even from hour to hour.[32]

SUBTENTORIAL STRUCTURAL LESIONS CAUSING COMA

Structural lesions of the posterior fossa cause coma either by destruction of the brainstem or by extrinsic compression. Destructive lesions must involve the paramedian reticular formation bilaterally to cause coma. Unlike small supratentorial lesions, small lesions of the brainstem can cause coma because of the discrete location of the ascending reticular activating system. Compressive lesions alter consciousness either directly, causing local brainstem dysfunction, or indirectly by herniation of the contents of the posterior fossa up through the tentorial notch or down through the foramen magnum.[33] The location of brainstem compression in midbrain, pons, or medulla determines the clinical features. Most compressive lesions of the posterior fossa causing coma arise in the cerebellum. Expanding cerebellar mass lesions typically cause defects in horizontal gaze, ocular bobbing, and other abnormal oculomotor signs. The pupillary light reflex is preserved, the pupils are miotic. The speed of evolution of structural lesions of the posterior fossa determines how much the level of consciousness is depressed. For example, slowly evolving destructive lesions of the brainstem such as primary tumors can cause striking neurologic deficits without producing coma, although lethargy may be prominent in the late stages. By contrast, acute destructive lesions, such as basilar artery thrombosis, often cause an abrupt loss of consciousness. Gradual compression of the brainstem can cause consider-

Table 4. *Clues to Subtentorial Structural Lesions as a Cause of Coma*

Loss of consciousness, abrupt or evolving
Focal brainstem signs precede or accompany onset of loss of consciousness
Signs indicate segmental brainstem dysfunction
Pupillary abnormalities frequent, oculomotor abnormalities invariable
Bilateral brainstem dysfunction but not necessarily complete or symmetric

able distortion and dysfunction with minimal alteration in the level of consciousness. In contrast, rapid deterioration in the level of consciousness occurs with acute compression caused by cerebellar hemorrhage, intraventricular extension of hemispheric hemorrhage, and so forth.

A number of clues suggest a posterior fossa structural lesion as the cause of coma (Table 4). Abrupt loss of consciousness suggests acute brainstem dysfunction. However, in addition to structural lesions of the posterior fossa, acute brainstem dysfunction also occurs in subarachnoid hemorrhage, parenchymal hemispheric hemorrhages that dissect into the ventricular system, trauma, seizures and anoxia.

Localized brainstem dysfunction usually implies the presence of a structural subtentorial lesion, either destructive or compressive. For example, a destructive lesion at the level of the mid pons can result in loss of horizontal gaze, absent caloric responses, and coma. While localized lesions sufficient to cause coma must involve both sides of the midline reticular formation, they need not necessarily produce either symmetric or complete damage to other functions anatomically represented at that level. Bilateral brainstem signs usually precede or accompany the onset of coma and do not evolve later as is the case with supratentorial lesions. If with stimulation the patient with injury to the brainstem can be aroused to answer questions, cognitive function is relatively normal, indicating integrity of the cerebral hemisphere. In the late stages of posterior fossa structural lesions, results of examination are indistinguishable from those seen in late transtentorial herniation, since in both conditions all brainstem function is absent.

The CT scan has revolutionized the diagnosis of intracranial structural lesions. Yet artifacts are frequent and one must preserve caution, particularly when studying the posterior fossa. Even a small amount of movement can obscure the contents of the posterior fossa. Artifact can also suggest the presence of a mass lesion of the posterior fossa to even the most experienced neuroradiologist. Thus, the information provided by the CT scan must be interpreted in light of the clinical features. If a structural process is suspected, general anesthesia may be required to eliminate artifact.

Specific Infratentorial Structural Lesions

The common and treatable structural lesions are either vascular lesions of the brainstem or extrinsic mass lesions. Basilar artery occlusion and cerebellar hemorrhages represent these two types of lesions.

Basilar artery occlusion is caused by emboli or thrombosis, both usually secondary to arteriosclerosis though rarely caused by vasculitis, valvular heart disease, fibromuscular dysplasia, and other entities. Basilar artery occlusion may be heralded by vertebrobasilar transient ischemic attacks.[40] In some patients the onset is abrupt, particularly when caused by emboli. Coma, dysarthria, abnormal pupils, and skew deviation of the eyes are prominent with the onset. The pupillary abnormality depends on the brainstem level of ischemia in the brainstem; small and reactive pupils indicate a pontine abnormality, midposition and unreactive pupils indicate position in the mid brain, and dilated and unreactive pupils indicate damage at the third nerve outflow level. Symptoms in a second group of patients evolve more slowly, over days or even weeks. The deterioration is usually step-like but can be gradual. The signs indicate multifocal brainstem dysfunction. Most patients are lethargic, delirious or stuporous. Coma is a late manifestation. Heparinization may limit the degree of brainstem injury.[14]

Abcesses, granulomas and neoplasms can also destroy the brainstem and impinge on the ascending reticular activating system. Since the evolution is slow, coma is a late manifestation of these destructive lesions.

Cerebellar hemorrhage, if recognized early, is a treatable potential cause of death.[5] Most cerebellar hemorrhages are associated with hypertensive vascular disease; the remainder occur with coagulopathies, anticoagulant therapy, or tumors. Approximately 20 per cent of patients suddenly lose consciousness, the examination indicating pontine and medullary dysfunction. In other patients, severe headaches, nausea, and vomiting develop, and progressive neurologic dysfunction, characterized by loss of oculovestibular reflexes, ataxic respiration, facial weakness, depressed corneal sensibility and, if the patient can be tested, ataxia and dysmetria, is seen. Vertical gaze and pupillary light reflexes are generally preserved. Hemiparesis is uncommon. Coma develops late. The rate of progression is variable and may range from 1 to 48 hours from onset to coma, rarely longer. Not all cerebellar hemorrhages are fatal if untreated.[15] However, in patients with rapidly progressive signs, surgery can be life-saving if performed early. Once the patient is in coma, surgery is of uncertain value.[5]

Cerebellar infarction presents with a constellation of signs and symptoms similar to those of cerebellar hemorrhage.[39] The features that distinguish cerebellar infarction from hemorrhage are infrequent headache and a slower progression to peak deficits, averaging 2 to 4 days. Surgical treatment can be life saving.

EMERGENCY TREATMENT OF RAISED INTRACRANIAL PRESSURE AND MASS EFFECT

As a reflection of raised intracranial pressure, compliance of the intracranial contents is decreased. Small changes in intracranial volume result in large changes in intracranial pressure. The preferred

method of reducing increased intracranial pressure and threatened herniation is specific therapy, for example, evacuation of a subdural hematoma. Such specific therapy may necessarily be delayed at times it may not be available. The nonspecific therapies available are osmotic agents, steroids, and hyperventilation. The effect of nonspecific therapy is to *delay* further brain swelling as the result of mass effect and subsequent herniation.

Osmotic agents reduce intracranial pressure by decreasing brain water content.[12] Administration of these agents creates an osmotic gradient between the plasma and brain; free water moves into the plasma. The dehydrating effect requires that a semipermeable membrane, the blood-brain barrier, be intact. Otherwise, the osmotic particles will be sequestered in the extracellular spaces. Incompetence of the blood-brain barrier occurs in trauma, some infarcts, tumors, and inflammatory lesions. In such circumstances, osmotic agents may in fact reduce intracranial pressure by dehydrating normal tissues.[31]

Osmotic agents are limited and short-lived in their therapeutic effect. Further removal of water requires a further increase in plasma osmolality; however, increases in blood osmolality above 330 mOsm will damage neural tissues. The peak reduction in intracranial pressure is at about 2 hours. It lasts for 4 to 6 hours. A rebound in intracranial pressure is prominent with urea.[31] It also occurs after administration of mannitol and glycerol.[26, 35] Rebound is caused by an increased brain parenchymal osmolality that exceeds plasma osmolality as the latter declines.[13]

The osmotic agents of choice are mannitol and glycerol. The dose of mannitol is 0.5 to 2 gm per kg given intravenously. The lowest effective dose should be employed. If crystals are present in the 25 per cent solution, they should first be dissolved by warming the solution, which is then infused through a filter. The dose can be repeated every 4 to 6 hours. Glycerol is given orally, usually through a nasogastric tube, also in doses of 0.5 to 2 gm per kg. During osmotic therapy, fluids, electrolytes, and intravascular fluid volume must be monitored. Hyperosmolar states can occur.

Steroids can substantially reduce the edema associated with primary and metastatic brain tumors and brain abcesses.[34] The agents have no demonstrated value in the treatment of stroke,[19] and uncertain effect in the treatment of head trauma.[11] The value of massively increasing the dose of steroids is similarly doubtful. When high-dose steroids are employed, most patients respond to conventional high doses, equivalent to 16 mg of dexamethasone per day.

Hyperventilation is the best emergency treatment for raised intracranial pressure.[18] The reduction in intracranial blood volume that accompanies hyperventilation often produces a rapid reduction in intracranial pressure which may occur within 10 to 15 seconds. However, intracranial pressure is not reduced in all patients and the effect is short-lived, usually lasting no more than an hour or so. Patients should be intubated, and the arterial partial pressure of carbon dioxide should be maintained between 20 and 25 mm Hg.

THE LUMBAR PUNCTURE

Before doing lumbar puncture, its risks must be weighed against its potential advantages. The three major risks of lumbar puncture are herniation, local hematoma formation, and introduction of pathogens. Diagnosis of acute infectious meningitis is the single overriding indication for lumbar puncture; in all other circumstances the procedure can be deferred at least until the clinical problem is thoroughly evaluated by less invasive procedures including CT scan.

DIFFUSE AND MULTIFOCAL CAUSES OF COMA

Accurate diagnosis of diffuse or multifocal causes of coma can be difficult. It is not always easy to recognize that the patient has a metabolic encephalopathy. Focal features may be present. Depression of central nervous system function may follow a rostral to caudal sequence. No single constellation of signs is uniformly diagnostic of diffuse (metabolic) central nervous system injury. In addition, the causes of diffuse central nervous system dysfunction are not limited to metabolic disorders (Table 5). Diseases of the subarachnoid space, e.g., bacterial meningitis and subarachnoid hemorrhage, and diffuse multifocal structural disease, can mimic metabolic encephalopathies. A potential diagnostic trap is presented by chronic subdural hematomas and other entraparenchymal mass lesions that can produce diencephalic dysfunction, drowsiness, and impaired cognition, often without prominent focal features. The post-ictal state as well as repetitive psychomotor or petit mal seizures can also mimic a metabolic encephalopathy.

Examination

The diagnosis of diffuse or multifocal central nervous system disease requires perspective and evaluation of all the clinical facts. The hallmark of coma caused by diffuse or multifocal disease is *the simultaneous onset of neurological dysfunction at multiple anatomic levels*. Historically, the onset is usually gradual, progressing through an acute confusional state. Initially, such patients appear preoccupied, lacking interest in their environment. With further deterioration, they become either stuporous or agitated. Prominent is the inability to maintain attention to a task. When answers do emerge the responses reflect slowed mentation, decreased insight, and confusion. Patients may be uncooperative, obscuring the change in mental status. Stuporous patients, when aroused, are restless, dysarthric, and blunted, relapsing into sleep when left unattended. Disorders of perception, illusions, and hallucinations are common. Hallucinations are usually visual, although auditory hallucinations occur with sufficient frequency that the symptom cannot be used categorically to differentiate between psychiatric and "organic" disease. The overall impression is that of a confused patient, unable to maintain focused contact with the environment.

Table 5. *Diffuse and Multifocal Causes of Coma**

A. Deprivation of oxygen, substrate, or metabolic cofactors
  1. Hypoxia (interference with oxygen supply to the entire brain—cerebral blood flow normal)
    a. Decreased oxygen tension and oxygen content in blood
      Pulmonary disease
      Alveolar hypoventilation
      Decreased atmospheric oxygen tension
    b. Decreased oxygen content of blood—oxygen tension normal
      Anemia
      Carbon monoxide poisoning
      Methemoglobinemia
  2. Ischemia (diffuse or widespread multifocal interference with blood supply to brain)
    a. Decreased cerebral blood flow resulting from decreased cardiac output
      Stokes-Adams syndrome; cardiac arrest; cardiac arrhythmias
      Myocardial infarction
      Congestive heart failure
      Aortic stenosis
      Pulmonary infarction
    b. Decreased cerebral blood flow resulting from decreased peripheral resistance in systemic circulation
      Syncope: orthostatic, vasovagal
      Carotid sinus hypersensitivity
      Low blood volume
    c. Decreased cerebral blood flow presumably due to generalized or multifocal increased vascular resistance
      Hypertensive encephalopathy
      Hyperventilation syndrome
      Hyperviscosity (polycythemia, cryoglobulinemia or macroglobulinemia, sickle cell anemia)
    d. Decreased cerebral blood flow due to widespread small vessel occlusions
      Disseminated intravascular coagulation
      Systemic lupus erythematosus
      Nonbacterial thrombotic endocarditis
      Subacute bacterial endocarditis
      Fat embolism
      Cerebral malaria
      Cardiopulmonary bypass
      Thrombotic thrombocytopenic purpura
  3. Hypoglycemia
    Resulting from exogenous insulin
    Spontaneous (endogenous insulin, liver disease, etc.)
  4. Cofactor deficiency
    Thiamine (Wernicke's encephalopathy)
    Pyridoxine
    Cyanocobalamin
B. Diseases of organs other than brain
  1. Diseases of nonendocrine organs
    Liver (hepatic coma)
    Kidney (uremic coma)
    Lung (carbon dioxide narcosis)
  2. Hyperfunction and/or hypofunction of endocrine organs
    Pituitary
    Thyroid (myxedema-thyrotoxicosis)
    Parathyroid (hypoparathyroidism and hyperparathyroidism)
    Adrenal (Addison's disease, Cushing's disease, pheochromocytoma)
    Pancreas (diabetes, hypoglycemia)

Table continued on following page

Table 5. *Diffuse and Multifocal Causes of Coma* (Continued)*

3. Other systemic diseases
   - Cancer (remote effects)
   - Porphyria

C. Exogenous poisons
1. Sedative drugs
   - Barbiturates
   - Nonbarbiturate hypnotics
   - Tranquilizers
   - Bromides
   - Ethanol
   - Anticholinergics
   - Opiates
2. Acid poisons or poisons with acidic breakdown products
   - Paraldehyde
   - Methyl alcohol
   - Ethylene glycol
   - Ammonium chloride
3. Enzyme inhibitors
   - Heavy metals
   - Organic phosphates
   - Cyanide
   - Salicylates

D. Abnormalities of ionic or acid-base environment of central nervous system
1. Water and sodium (hypernatremia and hyponatremia)
2. Acidosis (metabolic and respiratory)
3. Alkalosis (metabolic and respiratory)
4. Potassium (hyperkalemia and hypokalemia)
5. Magnesium (hypermagnesemia and hypomagnesemia)
6. Calcium (hypercalcemia and hypocalcemia)

E. Encephalitis
1. Viral
2. Multifocal bacterial (subacute bacterial endocarditis, sepsis)
3. Multifocal abscess (candida, aspergillus, others)
4. Multifocal parasites (toxoplasmosis)

F. Diseases of the subarachnoid space
1. Meningitis (septic, aseptic, and carcinomatous)
2. Subarachnoid hemorrhage
3. Granulomatous diseases (sarcoid, tuberculosis)

G. Extraparenchymal mass lesions
1. Hematomas (subdural or epidural)
2. Epidural abscess
3. Tumor

H. Epilepsy
1. Psychomotor or petit mal status
2. Post-ictal state

*Modified from Plum, F., and Posner, J. B.: Stupor and Coma. Philadelphia, F. A. Davis, 1972. By permission.

Several clinical features support the diagnosis of diffuse or multifocal central nervous system dysfunction (Table 6). Abnormalities in breathing, neuro-ophthalmologic and motor activities reflect dysfunction that is bilateral and present at multiple levels, yet is incomplete at any one level. Focal features are frequent, but asymmetries typically are minimal and fluctuate over time. (Rarely, focal features are prominent and persistent as in hypoglycemia.)

Table 6. *Clues to Diffuse or Multifocal Diseases Causing Coma*

Partial, bilateral dysfunction at many levels
Not necessarily uniform or symmetric
Gradual onset, preceded by an acute confusional state
Pupillary light reflex preserved
Asterixis, myoclonus
Diffuse paratonic resistance

Preserved pupillary reactions are the single most important sign differentiating metabolic from structural coma. The presence of preserved light reflexes despite concomitant respiratory depression, absence of oculovestibular reflexes or even decerebrate rigidity implies a metabolic cause. Conversely, if asphyxia or ingestion of glutethimide or *massive* amounts of barbiturates can be excluded, the absence of pupillary light reflexes strongly suggests that the coma results from a mass lesion.

The characteristic motor signs of diffuse central nervous system disease are a diffuse, "plastic" increased resistance to passive movement, tremor, asterixis, and multifocal myoclonus. The *tremor* is best observed in specific postures, for example with the arms outstretched. The tremor is coarse and irregular with a frequency of 8 to 10 cycles per second.

Asterixis is a sudden loss of voluntary effort. It is best observed by asking the subject to extend the arms and dorsiflex the hands. The earliest manifestation consists of small side to side twitches of the fingers. When more advanced, the fingers fall in a sudden downward jerk then gradually return to the original position, hence the descriptive term, "flap". The movement is bilateral, but it is asyncronous and irregular. Asterixis is observed in a wide variety of metabolic encephalopathies and occasionally in multifocal structural disease. When voluntary effort disappears, asterixis can no longer be elicited.

Multifocal myoclonus consists of a sudden, nonrhythmic, nonpatterned twitch of muscle motor units. Except for the fingers and toes, the force is usually not sufficient to cause movement across a joint. Multifocal myoclonus reflects a serious metabolic disturbance.

Management

If it is suspected that coma results from diffuse or multifocal injury to the central nervous system, blood should be drawn for metabolic studies, especially for electrolytes, arterial blood gases, and glucose. Urine and blood should be reserved for toxicologic examination. As outlined above, the immediate priority is to treat hypoxia and hypoglycemia. Thereafter, disorders which can cause death or further central nervous system injury in a brief period of time should be considered. These include electrolyte imbalance, metabolic acidosis, thiamine deficiency, and bacterial meningitis. Alcoholics and others suspected of nutritional deficiency should be given 50 mg of thiamine intramuscularly since administration of carbohydrate can precipitate Wernicke's

encephalopathy. A lumbar puncture must be rapidly performed on all patients exhibiting fever and meningitis. If the underlying cause is still uncertain, the evaluation can proceed deliberately, giving full attention to the different possible diagnoses listed in Table 5. During this evaluation, the patient should be monitored closely, with attention to vital signs, fluid balance, and pertinent signposts in the neurologic examination.

The treatment of drug overdose deserves special comment. Overingestion of drugs accounts for the majority of cases of metabolic coma presenting to a general hospital. Furthermore, the central nervous system dysfunction that accompanies drug ingestion is almost always reversible if the patient survives long enough to reach the hospital. The overriding principle of management is to provide respiratory and cardiovascular support by the simplest possible means.[3]

Several techniques can reduce the amount of drug absorbed from the gastrointestinal tract. In *alert* patients, vomiting can be induced by syrup of ipecac. In *drowsy* or *stuporous* patients, gastric lavage should be performed but only *after* endotracheal intubation, since an impaired cough reflex can otherwise lead to pulmonary aspiration. Since sedative and cholinergic drugs delay gastric emptying, lavage performed hours after ingestion may remove unabsorbed drug. Activated charcoal nonspecifically binds many durgs, preventing absorption.[6] After gastric lavage, 50 to 200 mg of activated charcoal should be instilled into the stomach.

Patients who can be aroused to purposeful movements and vocalization may still suffer cerebral depression and even respiratory arrest when left unattended. If there is any doubt about the amount of drug ingested, the patient should be admitted and followed closely, preferably in an intensive care setting.

Forced diuresis, hemodialysis, and hemoperfusion speed removal of some drugs. However, the advantages of these techniques over conventional intensive care has not been established except in instances of severe poisoning with long-acting drugs such as phenobarbital and rarely glutethimide.

PSYCHOGENIC UNRESPONSIVENESS

The physician should make the diagnosis of hysteria with caution, particularly in the unresponsive patient. Psychogenic unresponsiveness rarely lasts for more than a few minutes. The diagnosis requires demonstration of intact function of the brainstem reticular formation and hemispheres.[16] In psychogenic unresponsiveness, caloric testing produces quick phase nystagmus away from the cold water irrigation. The eyes are usually forcefully (voluntarily) closed. The pupillary light reflex is normal. If doubt persists, a normal awake electroencephalogram helps to confirm the diagnosis.

The differentation between catatonic stupor and "organic" stupor is more difficult. Catatonic patients appear obtunded rather than co-

matose, a state compatible with normal oculovestibular and pupillary reflexes. The electroencephalogram can be midly abnormal. The typical appearance is that of a subject lying immobile with open eyes, a rapid pulse, and normal or rapid respiration. Dilated pupils and alternating anisocoria may be present. Incontinence is common. Caloric responses are normal. This typical appearance in a young patient recently exposed to an emotionally upsetting experience suggests the diagnosis. Sedation by intravenous barbiturates (Amytal interview) often supports the diagnosis.[30] With such sedation, catatonic patients will eventually begin to respond to the environment. By contrast, "organic" patients will have one metabolic insult, i.e., sedation, superimposed on another and, in consequence, will rapidly become more deeply stuporous.

REFERENCES

1. Adams, R. D., and Victor, M.: Principles of Neurology, New York, McGraw-Hill Book Company, 1977, pp. 264–266.
2. Albert, M. L., Silverberg, R., Reeches, A., et al.: Cerebral dominance for consciousness. Arch. Neurol., *33*:453–454, 1976.
3. Benowitz, N. L., Rosenberg, J., and Becker, C. E.: Cardiopulmonary catastrophies in drug-overdosed patients. Med. Clin. N. Amer., *63*:267–296, 1979.
4. Berger, A. J., Mitchell, R. A., and Severinghaus, J. W.: Regulation of respiration. New Eng. J. Med., *297*:92–97, 138–143, 194–201, 1977.
5. Brennan, R. W., and Bergland, R. M.: Acute cerebellar hemorrhage. Neurol., *27*:527–532, 1977.
6. Corby, D. G., and Decker, W. J.: Management of acute poisoning with activated charcoal. Pediatrics, *54*:324–328, 1974.
7. Della Porta, P., Maiolo, A. T., Negri, V. U.: Cerebral blood flow and metabolism in the therapeutic insulin coma. Metabolism, *13*:131–140, 1964.
8. Ducker, T. B., Simmons, R. L., and Anderson, R. W.: Increased intracranial pressure and pulmonary edema. Part 3: The effect of increased intracranial pressure on the cardiovascular hemodynamics of chimpanzees. J. Neurosurg., *29*:475–483, 1968.
9. Duffy, G. P.: Lumbar puncture in the presence of raised intracranial pressure. Brit. Med. J., *1*:407–409, 1969.
10. Edelson, R. N., Chernik, N. L., and Posner, J. B.: Spinal subdural hematomas complicating lumbar puncture. Occurrence in thrombocytopenic patients. Arch. Neurol., *31*:134–137, 1974.
11. Faupel, G., Reulen, H. J., Muller, D., et al.: Double-blind study on the effects of steroids on severe closed head injury. *In* Pappius, H. M., and Feindel, W., eds.: Dynamics of Brain Edema. Heidelberg, Springer-Verlag, 1976, pp. 337–343.
12. Fishman, R. A.: Brain edema. New Eng. J. Med., *293*:706–711, 1975.
13. Fishman, R. A.: Cell volume, pumps and neurologic function: Brain's adaption to osmotic stress. Res. Publ. Assoc. Nerv. Ment. Dis., *53*:159–171, 1974.
14. Genton, E., Barnett, H. J. M., Fields, W. S., et al.: Cerebral ischemia: the role of thrombosis and of antithrombotic therapy. Stroke, *8*:150–175, 1977.
15. Heiman, T. D., and Satya-Mutyi S.: Benign cerebellar hemorrhages. Ann. Neurol., *3*:336–368, 1978.
16. Hopkins A.: Pretending to be unconscious. Lancet, *2*:312–313, 1973.
17. Jamieson, K. G., and Yelland, J. D. N.: Extradural hematoma. Report of 167 cases. J. Neurosurg., *29*:13–23, 1968.
18. James, H. E., Langfitt, T. W., Kumar, V. S., et al: Treatment of intracranial hypertension. Analysis of 105 consecutive continuous recordings of intracranial pressure. Acta Neurochir., *36*:189–200, 1977.
19. Katzman, R., Clausen, R., Klatzo, I., et al.: Report of Joint Committee for Stroke Resources. IV. Brain edema in stroke. Stroke, *8*:512–540, 1977.
20. Keane, J. R.: Ocular skew deviation. Arch. Neurol., *32*:185–190, 1975.
21. Korein, J., Cravioto, H., and Leicach, M.: Reevaluation of lumbar puncture. A study of 129 patients with papilledema or intracranial hypertension. Neurology, *9*:290–297, 1959.

22. Laglia, A. G., Eisenberg, R. L., Weinstein, P. R., et al.: Spinal epidural hematoma after lumbar puncture in liver disease. Ann. Intern. Med., *88*:515–516, 1978.
23. Leigh, J. R., and Shaw, D. A.: Rapid regular respiration in unconscious patients. Arch. Neurol., *33*:356–361, 1976.
24. Lipowski, Z. J.: Delirium, clouding of consciousness and concussion. J. Nerv. Ment. Dis., *145*:227–255, 1976.
25. Lubic, L. G., and Marotta, J. T.: Brain tumor and lumbar puncture. Arch. Neurol. Psychiatry, *72*:568–572, 1954.
26. McQueen, J. D., and Jeanes, L. D.: Dehydration and rehydration of the brain with hypertonic urea and mannitol. J. Neurosurg., *32*:118–128, 1964.
27. Miller, J. D., Stanek, A. and Langfitt, T. W.: Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension. Prog. Brain Res., *35*:411–432, 1972.
28. Miller, J. R., and Meyers, R. E.: Neurological effects of systemic circulatory arrest in the monkey. Neurol., *201*:715–724, 1970.
29. Moruzzi, G., and Magoun, H. W.: Brainstem reticular formation and activation of the EEG. Electroenceph. Clin. Neurophysiol., *1*:445–473, 1949.
30. Naples, M., and Hackett, T. P.: The Amytal interview: History and current uses. Psychosomatics, *19*:98–105, 1978.
31. Pappius, H. M., and Dayes, L. A.: Hypertonic urea. Its effect on the distribution of water and electrolytes in normal and edematous brain tissues. Arch. Neurol., *13*:395–402, 1965.
32. Pevehouse, B. C., Bloom, W. H., and McKissock, W.: Ophthalmologic aspects of diagnosis and localization of subdural hematomas. Neurology, *10*:1037–1041, 1960.
33. Plum, F., and Posner, J. B.: Stupor and Coma. Philadelphia, F. A. Davis Co., 3rd ed., in press.
34. Posner, J. B.: Diagnosis and management of metastases to the brain. Clin. Bull., *4*:45–57, 1974.
35. Rottenberg, D. A., Hurwitz, B. J., and Posner, J. B.: The effect of oral glycerol on intraventricular pressure in man. Neurol., *27*:600–608, 1977.
36. Salford, L. G., Plum, F., and Brierley, J. B.: Graded hypoxia-oligemia in rat brain: II. Neuropathological alterations and their implications. Arch. Neurol., *29*:234–238, 1973.
37. Schumacher, G. A., and Wolff, H. G.: Experimental studies on headache. Arch. Neurol. Psych., *45*:199–214, 1941.
38. Senelick, R. C., Norwood, C. W., and Cohen, G. H.: "Painless" spinal epidural hematoma during anticoagulant therapy. Neurol., *26*:213–215, 1976.
39. Sypert, G. W., and Alvord, E. C., Jr.: Cerebellar infarction. A clinicopathological study. Arch. Neurol., *32*:363, 1975.
40. Williams, D., and Wilson, T. G.: The diagnosis of the major and minor syndromes of basilar insufficiency. Brain, *85*:741–774, 1962.

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Treatment of Primary Brain Tumors

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The patient with a brain tumor is a source of both interest and helplessness to the nonspecialist involved in his care. This dual outlook arises because the nonspecialist sees the patient with a brain tumor at the two extremes of his course: at the beginning, when the patient presents with a fascinating array of symptoms suggesting a brain tumor; and at the end, when the patient, after surgery, radiation, and chemotherapy, presents as an apathetic mute who quickly lapses into coma and dies. What is not appreciated is that between these extremes a therapeutic revolution is occurring and more patients are living longer, more normal lives. The purpose of this review is to make the nonspecialist aware of this revolution.

There are 385,000 deaths from cancer each year and 50,000 (13 per cent) are associated with central nervous system involvement. It is estimated that of these 50,000 deaths, 8500 (17 per cent) are caused by primary brain tumors and 5000 of these are caused by malignant gliomas. The number of deaths from malignant gliomas exceeds the number of deaths from Hodgkin's disease.[41]

Statistics on the prevalence of the different types of primary brain tumors vary depending upon the institution and the type of series: surgical or postmortem. At New York University-Bellevue Medical Center, in 20 years (1956 to 1978), there were 1100 surgically verified supratentorial tumors. Among them, 150 were metastatic and 950 were primary brain tumors including 480 glial tumors, 300 meningiomas, and 100 pituitary adenomas. Among the 480 glial tumors, 400 (83 per cent) were astrocytomas, of which 310 were malignant astrocytomas (grades 3 or 4); 50 (10 per cent) were mixed tumors; 18 (4 per

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cent) were oligodendrogliomas, and 11 (2 per cent) were ependymomas. The figures on supratentorial glial tumors are in agreement with those of others.[11, 36]

Patients with brain tumors are encountered in three separate circumstances. In the first, the patient presents with a brain tumor and no history of systemic cancer. Work-up in most institutions will as likely reveal the tumor to be metastatic as primary. In the second instance the patient presents with a brain tumor and a past history of systemic cancer. Work-up in this setting almost always reveals the tumor to be metastatic. In the third instance, a patient with obvious systemic cancer develops a brain tumor that on work-up is invariably metastatic.

CLASSIFICATION

Most classifications of brain tumors emphasize the embryogenesis of the various cellular components of the central nervous system and attempt to classify the tumors in terms of the different morphologic stages which the cells pass through during oncogenesis. Tumors are classified into those of astroglial, oligodendroglial, ependymal and neuronal series.[11, 36] The glioblastoma is conceived of as taking origin de novo from a primitive stem cell, the glioblast. Occasionally, it is conceived of as originating from an astrocytoma and is referred to as a secondary glioblastoma.[11, 19] Recently, the tendency has been to downplay the concept of embryogenesis and to emphasize the importance of anaplasia. Glial tumors, like neoplasms elsewhere in the body, undergo increasing anaplasia and their classification has been simplified into astrocytomas, oligodendrogliomas or ependymomas of varying grades of malignancy. Criteria for malignancy are: the degree of cellularity, pleomorphism, vascular hyperplasia, necrosis, and presence of mitotic figures.[19] This review will concern itself largely with glioblastomas, herein referred to as malignant astrocytomas (grade 3 or 4).

MALIGNANT ASTROCYTOMAS

Malignant astrocytoma has its peak incidence between the ages of 40 and 60; affects males more than females in a ratio of 3 to 2; and usually arises in the white matter of the frontal and temporal lobes, although it may occur anywhere in the brain. However, malignant gliomas arising in the pons, cerebellum, and spinal cord constitute less than 5 per cent of these tumors.[19, 36, 39] Malignant astrocytomas treated only with surgery result in death in 50 per cent of patients within 4 months, 90 per cent within 18 months, and virtually 100 per cent within 24 months. The tumors grow diffusely and do not form a capsule. They kill either by continued local growth or by spread along neural pathways such as the corpus callosum, 66 per cent having spread grossly or microscopically at the time of surgery.[7, 16, 28, 37, 39] About 5 per cent of malignant astrocytomas are multifocal, showing

either macroscopic or microscopic continuity with other tumor centers, and approximately 2 per cent of tumors are multicentered with no macroscopic or microscopic continuity between centers.[19] Multifocal and multicentric gliomas may be mistaken clinically and radiologically for metastasis. The tumor may occasionally reach the surface and infiltrate the leptomeninges resulting in freely circulating cells capable of implanting at distal sites.[1, 9, 31] The tumors virtually never metastasize outside the central nervous system in the absence of surgery.[10, 15] The reasons for this are: the absence of lymphatic channels in the brain; the presence of a tough dura and venous channels which are difficult for the tumor to penetrate; and the poor growth of the tumor outside the brain. The common sites of metastases, when they occur, are lung, liver, lymph node, and bone. Although meningitic spread and extracranial metastases are now of little importance, they may be of great importance once better control of the primary site is achieved.

OTHER PRIMARY SUPRATENTORIAL TUMORS

Neuronal tumors are embryonal tumors arising in nests of primitive multipotential cells which normally mature and differentiate into neurons, but may become neoplastic at any stage in their development. They are relatively rare.[10] Oligodendrogliomas consist of small round cells surrounded by relatively unstained cytoplasm constituting a halo over each cell. They are relatively avascular, and have a tendency to encapsulate, calcify, and form small cysts. They occur deep in the white matter and exhibit little tendency to invade adjacent brain tissue. Up to 70 per cent occur in the frontal lobes. A smaller number are seen in other sites including the third ventricle, the brain stem and cerebellum. Growth is slow, with the interval between the first symptom and surgical intervention averaging 24 to 70 months. Rarely, they become malignant.[2]

Ependymomas are tumors of children and young adults, and are predominantly infratentorial with the most common site being the fourth ventricle. In adults, they are as likely to be supratentorial as infratentorial. They are densely cellular with oval nuclei and scant cytoplasm. Different histologic patterns occur at different sites. The most common pattern seen in the ependymomas arising in the cerebrum and the fourth ventricle consists of uniformly arranged cells about blood vessels forming perivascular clear spaces devoid of nuclei (rosettes). In another pattern seen in the ependymomas arising from the cerebellopontine angle, the cells are distributed about blood vessels in a papillary arrangement. In a third pattern found among the ependymomas of the cauda equina, myxomatous degeneration occurs. Ten per cent of ependymomas may seed along the meninges.[12, 21]

"Mixed tumors" consist of two or more glial cell types. They may be compact with discrete areas of each type of tumor existing side by side, or they may be diffuse and infiltrative with intermingling of each cell type. The majority of mixed tumors are combinations of oligodendro-

gliomas and astrocytomas. The next most common combination is oligodendroglioma and ependymoma.[15] These tumors may arise because two or more glial cells become neoplastic simultaneously, an occurrence also encountered in some chemically induced tumors. On the other hand, one glial cell may differentiate along the lines of another glial cell; or one glial cell may induce neoplastic transformation in an adjacent glial cell or occasionally in a nonglial or mesenchymal cell. Thus, the proliferation of vascular endothelium in an astrocytoma may occasionally progress to a sarcoma, producing a picture of a gliosarcoma.[29] Mixed tumors, although rare, may provide us with unique clues in understanding neoplastic transformation in the brain.

DIAGNOSIS

The diagnosis of a brain tumor depends upon the correlation of symptoms and signs with neuroradiologic findings. The most common symptoms of a brain tumor are headache (occurring in 30 per cent of patients); seizures (occurring in 20 per cent); personality changes, and motor and speech disturbances. When focal deficits are progressive for several weeks or months, they are usually indicative of a brain tumor. Symptoms of malignant brain tumors are usually present for less than a year before diagnosis. Similar symptoms of more than a year's duration generally indicate a less malignant tumor. The diagnosis of brain tumor has been markedly facilitated by computed tomography (CT). In one study, 96 per cent of all clinically symptomatic gliomas were detected by CT scan in comparison to 78 per cent detected by brain scan, 75 per cent by angiogram, and 80 per cent by clinical assessment. Four per cent of malignant gliomas were not detected by CT scanning. Rarely, false positive scans were noted when infarcts or scan artifacts were interpreted as tumors.[1] Angiography is now seldom required for diagnosis, but it is usually required for surgery. The isotopic brain scan may be useful when a tumor, suspected clinically, is not detected by CT scan or when a lesion on CT scan is suspected of being artifact. Lumbar puncture, aside from the risks of herniation in the presence of an intracranial mass lesion is frequently abnormal but seldom diagnostic;[4] it is still, however, the only way of making a diagnosis of meningeal involvement. The electroencephalogram, though useful in the past, has with the advent of CT scanning, become much less important as a screening procedure.

SURGERY

No controlled study has been done comparing the efficacy of surgical and nonsurgical therapy in the treatment of malignant glioma. However, there is reasonable evidence that patients who have had surgery do better than patients who have not.[13, 20, 32, 34] Given the accuracy of currently available diagnostic studies, surgery rarely has to be done

solely for diagnostic purposes. Much of the resistance to surgery stems from an earlier era in which it was associated with a mortality of 20 per cent.[3] Marked improvements in anesthetic techniques and the use of corticosteroids to decrease brain swelling has reduced the mortality to under 2 per cent. In addition, accurate preoperative localization with the CT scanner combined with the operative microscope has allowed for a more radical approach.[32] On the basis of careful planning, radical tumor surgery may be carried out at almost every intracranial location other than the deep central areas of the dominant hemisphere, the posteriorly located corpus callosum, and the upper brain stem, with a reasonable chance of achieving significant removal of tumor without neurologic injury. Surgery has usually been confined to subtotal resection shortly after the time of diagnosis, and second operations after radiation therapy, chemotherapy, or both are now rarely performed. However, when such operations have been undertaken, greater containment of the tumor is noted and the core of necrotic tumor may be more completely excised. Delayed surgery with preoperative radiotherapy and chemotherapy in other cancers has some suggestive value, and is now being investigated as part of a randomized prospective study by the Brain Tumor Study Group.

The role of surgery is much better established in patients with low grade tumors where complete resection is often possible, and cure may be achieved.

RADIATION THERAPY

Although radiation therapy for central nervous system tumors has been utilized for over 40 years, until recently, there was controversy as to its effectiveness. Because of the nature of malignant gliomas and their extensive microscopic spread outside the surgical field, radiotherapy with limited ports and low dosages had been ineffective. Utilizing large ports and dosages between 5500 and 6000 rads, a distinct advantage to radiation therapy has been demonstrated. Radiation therapy increases median survival of patients with malignant gliomas, but does not cure the tumor.[7, 37, 46, 49, 50] Although radiation dosages in this review (for historical purposes) are expressed in rads, current practice refers to units of radiation therapy in terms of the Nominal Standard Dose (NSD) in rets:

$$NSD = TD \div N^{0.24} \times T^{0.11}$$

where TD is the total dose, N is the number of treatments, and T is the number of days.

The role of radiation therapy in the treatment of less malignant tumors — astrocytomas, oligodendrogliomas, and ependymomas — is not as well established since no controlled prospective randomized studies have been done. However, in studies that are available, there is evidence of increased survival and delay in tumor recurrence in patients receiving radiation therapy.[27]

The malignant glioma is characterized by necrotic areas, particularly toward the center where cells grow in a relatively hypoxic environment and are protected by their location against the effects of radiation, a treatment which is more effective in the presence of oxygen. In addition, cell necrosis leads to the liberation of lysosomal enzymes resulting in edema which in turn results in more anoxia because of decreased diffusion of blood to the necrotic areas. Finally, vascular shunts within the tumor create additional islands of hypoxic tumor cells.

A small controlled study has indicated the value of the 5-nitroimidazole compound, metronidazole, in sensitizing hypoxic tumor cells to radiation.[47] The 2-nitroimidazole compound, misonidazole, appears to be even more effective.[51] Suprafractionation, i.e., more than one dose of radiation therapy per day, has a theoretic advantage over single daily treatments and has been explored in a preliminary study.[8] Suprafractionation increases the oxygen enhancement ratio of hypoxic tumor cells rendering them more susceptible to radiation therapy. Additionally, the rates of repopulation and repair of tumor cells compared to normal cells are such as to make them more sensitive to suprafractionated radiation. Both radiation sensitizers (misonidazole) and suprafractionation are currently under investigation by the Brain Tumor Study Group.

Another development in radiation therapy is the use of fast neutron as opposed to standard gamma-irradiation. In a recently concluded study, such irradiation led to massive coagulation necrosis adjacent to the operative site with no visible tumor tissue. However, these patients also developed marked radiation necrosis in normal adjacent tissue. Although there was no improvement in the length or quality of survival among these patients, the relative absence of tumor suggests that continued efforts to refine this mode of radiation therapy are warranted.[43]

CHEMOTHERAPY

Much of our understanding of the choice of chemotherapeutic agents and their penetration into and effect on the tumor comes from animal models. While such models, using induced or transplanted animal tumors, are inherently imperfect for understanding spontaneously arising human brain tumors, they nonetheless have broadened our understanding of the oncogenic process.[18, 54] Nitrosoureas (currently our best drugs) were developed with the mouse L1210 leukemia model.[38] Further understanding has come from using solid autochthonous central nervous system tumors such as those induced by carcinogens or oncogenic RNA viruses. Although the majority of such solid tumors show only some aspects of the highly variable spectrum of spontaneous human gliomas, their growth characteristics and response to chemotherapy resembles somewhat the situation in man. A recent and promising development has been the successful transplantation of

human malignant gliomas into nude (immunologically deficient) mice, permitting studies on the response of individual human tumors to chemotherapy.[42]

The blood-brain barrier must be taken into account in the design of chemotherapeutic agents for central nervous system tumors. Based on studies of meningeal leukemia, the chemotherapeutic agents for use in solid brain tumors were thought to be limited to small molecules of high lipid solubility and minimal ionization: properties promoting the diffusion across the blood-brain barrier.[28] Evidence from both animal models and clinical studies suggest that, in fact, there are no significant barriers to the entry of most drugs into the bulk of the malignant brain tumor.[21, 11, 18] Thus, radioisotopes and iodinated dyes readily cross into the tumor while failing to enter the surrounding brain tissue. In fact, such penetration represents the way tumors are diagnostically delineated from surrounding brain. The blood-brain barrier consists of the junction between the capillary endothelial cells and the adjacent glial or tumor cell processes. It has been shown that within the center of a primary brain tumor the capillaries of the tumor, and to a lesser extent the capillaries of the brain adjacent to the tumor, have structural abnormalities in their endothelium associated with an increased permeability to large molecules.[18] Approximately 90 per cent of a malignant brain tumor does not have a functional barrier, while the remaining 10 per cent of the tumor existing as clusters of cells in the brain adjacent to the tumor has a partial barrier. Thus, within the center of a brain tumor there is essentially ready access of both water and lipid soluble drugs to the tumor, while in the brain adjacent to the tumor there is a "partial" barrier to some drugs. The critical factors determining the success of chemotherapeutic agents in the center of the tumor are not their lipid solubility or molecular weight, but their migration across the tumor cell, metabolism within the cell, and inherent oncolytic activity. The factors determining the success of chemotherapeutic agents in the brain adjacent to the tumor includes, in addition to all of the above, the ability to penetrate the blood-brain barrier. Additionally, the activity of these agents is affected by the decrease in transcapillary exchange that occurs in the brain adjacent to the tumor. This decrease results from the increased hydrostatic pressure that opposes the movement of drugs from blood to brain adjacent to the tumor; from the reduction in extracellular space secondary to cellular edema; and/or from changes in endothelial cells secondary to compression or tumor metabolites. In the brain adjacent to the tumor, large molecular weight or water soluble molecules may not achieve adequate concentrations in tumor cells.

Although most chemotherapy has been devised without cytokinetics, such studies using radiolabelled thymidine should lead to more rational and effective drugs and schedules.[17, 19] Tumor growth correlates better with the growth fraction, the ratio of proliferating cells to total number of cells, than with the length of the cell cycle. Compared to other solid tumors, malignant gliomas exhibit a low growth fraction averaging 0.28 with a range of 0.14 to 0.40. The cell-cycle time is 24

to 48 hours and the duration of DNA synthesis (S Phase) is 4.5 to 10.5 hours. The birth rate, the number of newly formed cells per 100 tumor cells per hour, is 0.5 to 1.5. The time required for a given number of tumor cells to replicate their population in malignant gliomas is 4 to 8 days, assuming no cell loss. However, assuming a cell loss of 85 per cent, the doubling time of malignant gliomas is approximately 40 to 55 days, which correlates with clinical observations.

In order to critically evaluate chemotherapeutic agents in man, well designed prospective randomized studies involving a sufficiently large number of patients to achieve statistical validity are required. The Brain Tumor Study Group (BTSG) of the National Cancer Institute, a cooperative multi-institutional group, was organized to accomplish this task through a series of carefully designed Phase III Studies, each involving at least 300 patients and taking at least 3 years to complete.

The first BTSG Phase III Study (BTSG 66–01) evaluated mithramycin.[49] Although there was no significant difference in survival in those receiving mithramycin as compared to those not receiving mithramycin, this study demonstrated the ability of a large multicentered group to accumulate and randomize sufficient numbers of cases to determine statistical significance, study them according to a uniform protocol, develop accurate recording procedures, and cooperate in the evaluation of treatment.

The second BTSG Phase III Study (BTSG 69–01), evaluated 1-3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) and radiotherapy in the treatment of malignant glioma.[50]

A total of 303 patients were admitted into this study for random treatment allocation. Of these, 222 (73 per cent) were in the valid study group having met the criteria of neuropathologic diagnosis, corticosteroid control, and therapeutic approach. Patients were randomly allocated to four treatment groups. They received BCNU, 80 mg per sq meter of body surface area per day on three successive days, every 6 to 8 weeks; and/or radiation therapy, 5000 to 6000 rads of whole brain irradiation through bilateral opposing ports; or best conventional care without chemotherapy; or radiation therapy. Median survival of patients in the valid study group was: best conventional care — 14 weeks; BCNU alone — 19 weeks; radiation therapy — 35 weeks; and BCNU plus radiation therapy — 35 weeks. There were no significant differences among the four groups in age, sex, location of tumor, tumor characteristics, clinical signs and symptoms, or dose of corticosteroids. An analysis of prognostic factors indicated that the initial performance status as evaluated on the Karnofsky rating scale (Table 1) was significant. The usefulness of radiation therapy was unequivocally demonstrated in this study, increasing median survival by 150 per cent. The addition of BCNU to radiation therapy, although it failed to alter median survival, resulted in an increased number of patients living more than 18 months compared to patients receiving radiotherapy alone. The quality of survival among patients receiving radiotherapy alone or radiotherapy combined with BCNU was very good. The ma-

Table 1. *Karnofsky Rating Scale*

100	Normal.
90	Able to carry on normal activity. Minor symptoms.
80	Normal activity with effort. Some symptoms.
70	Cares for self. Unable to carry on normal activity.
60	Requires occasional assistance. Care for most needs.
50	Requires considerable assistance and frequent care.
40	Disabled. Requires special care and assistance.
30	Severely disabled. Hospitalized.
20	Very sick. Active supportive treatment needed.
10	Moribund.

jority returned to work or remained independent in activities of daily living (Karnofsky rating of at least 70).

The third BTSG Phase III Study (BTSG 72–01) compared methyl-1-(2-choroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl CCNU) alone to radiotherapy alone (6000 rads), methyl CCNU combined with radiotherapy, and BCNU combined with radiotherapy. The median survival for combined therapy (nitrosourea plus radiotherapy) approched statistical significance when compared to chemotherapy or radiotherapy alone. Among patients receiving the full course of radiotherapy and two or more courses of chemotherapy (adequately treated group), the figures for BCNU combined with radiotherapy reached statistical significance and 18 month survival exceeded 30 per cent. Quality of survival among patients remained very good with the majority resuming work or remaining independent throughout most of their treatment.

Morphologic changes in tumor tissues have been demonstrated in patients treated with BCNU alone. These consist of an increase in the number of giant cells with a decrease in the number of mitotic figures.[14, 53] These changes have been interpreted as the result of inhibition of cell division. The immediate toxicity of BCNU includes nausea, vomiting, flushing, transient rashes, and diarrhea; none of these effects are unusually severe. Delayed toxicity is usually mild, consisting of thrombocytopenia in 3 weeks, leukopenia in 4 weeks, and a drop in hematocrit at 5 weeks. Immediate hepatic, renal, and pulmonary toxicity is rare. However, there are reports of serious pulmonary fibrosis resembling that seen with bleomycin and busulfan as well as interstitial nephritis with repeated (more than 5) courses of the drug.

The improvement in survival among patients receiving BCNU combined with radiotherapy in BTSG 72–01 (median survival of 52 weeks) compared to the same group in the earlier BTSG 69–01 (median survival of 35 weeks) is attributable to the more aggressive use of BCNU in the later study, which included administering more courses and not modifying individual courses because of what were now recognized as relatively minor adverse effects. Such results indicate the need for internal controls and highlight the difficulties in comparing results from among institutions without a centrally directed uniform protocol. Thus, it is easy to understand why small studies, although

well designed, often give contradictory results.[33, 52] Such studies serve as pilots and suggest theoretical approaches, but cannot demonstrate the statistical validity of a particular treatment.

The fourth and most recently completed study, BTSG 75–01 evaluated the potential oncolytic effect of corticosteroids and compared them to BCNU and procarbazine. Corticosteroids have been shown to ameliorate neurologic signs and symptoms in more than 70 per cent of patients with brain tumors, both primary and metastatic. Onset of their reaction is rapid (24 to 48 hours), but it is usually short-lived (3 to 6 months). Response is independent of the type of steroid if equivalent doses are used. The rapid onset of neurologic improvement, the similarity of improvement in patients with different types of tumors, and the failure to note regression of any primary extracerebral tumor led most investigators to postulate that improvement with steroids was secondary to a reduction in cerebral edema.[25] Additionally, despite their often dramatic effect, there was no evidence that corticosteroids extended the survival of patients with brain tumors. However, both morphologic abnormalities and reduced growth rates have been noted in tissue cultures of biopsied human central nervous system tumors and in vivo studies in certain mouse tumors at high concentrations of steroids.[25] So suggestive was this evidence for tumor inhibition and/or oncolysis by steroids that the BTSG undertook a cooperative study to investigate this phenomenon.

Patients, after surgery and radiotherapy (6,000 rads) were divided into four groups. One group received BCNU, one received procarbazine, one received high dose intermittent corticosteroid (methylprednisolone, 400 mg/M^2/day for one week out of every three), and the fourth group received a combination of high dose intermittent corticosteroids and BCNU. Although this study has not yet been fully analyzed, it does not appear that corticosteroids cause tumor inhibition and/or oncolysis. Adverse effects on high dose intermittent methylprednisolone were surprisingly modest (compared to what had been anticipated), with an incidence of serious infections, gastrointestinal bleeding, myopathy, and endocrine abnormalities of well under 5 per cent. The fifth and current BTSG Phase III Study (BTSG 78–01) is evaluating conventional fractionated radiotherapy (6000 rads) combined with BCNU in contrast to suprafractionated radiotherapy combined with BCNU versus conventionally fractionated radiotherapy combined with the radiation sensitizer misonidazole plus BCNU and conventional radiotherapy combined with streptozotocin.

Because of the long time period required to evaluate a drug in a Phase III Protocol as well as the necessity to screen drugs before admission to such studies, Phase II Studies were developed. These studies admit patients with primary brain tumors who are not eligible for the more carefully controlled Phase III Studies. Phase II Studies also admit patients with metastatic tumors as well as those with inoperable tumors. Patients in the Phase II Studies are stratified into primary or metastatic tumor groups exhibiting similar ratings on the Karnofsky scale. All patients receive appropriate radiotherapy. The first such study, BTSG 72–20, evaluated four separate chemotherapeutic agents: adriamycin, dibromodulcitol, procarbazine, and streptozotocin. Two of

these agents, procarbazine and streptozotocin, were found worthy of more extensive evaluation. Procarbazine was evaluated in a subsequent Phase III Study (BTSG 75–01). Preliminary indications suggest that the drug is less effective than BCNU. Streptozotocin, a water-soluble nitrosourea, was re-evaluated in the second BTSG Phase II Study (BTSG 76–20) with three other agents: hydroxyurea, epipodophylotoxin, and a combination of methyl CCNU and procarbazine. Streptozotocin was sufficiently promising to be included in the fifth BTSG Phase III Study (BTSG 78–01) now in progress. The third and current BTSG Phase II Study (BTSG 77–20) is evaluating four separate treatments: chlorozotocin, a water-soluble nitrosourea with marrow sparing activity; triazinate, a diaminopyrimidine folic acid antagonist similar to methotrexate, but which (unlike methotrexate) concentrates in the brain; cis-diaminedichloroplatinum (cisplatinum), an inorganic chelated heavy metal complex with demonstrated antitumor activity in a variety of tumors; and, a combination of BCNU followed by 5-fluorouracil. This last combination represents a rational attempt to apply basic principles of cancer chemotherapy by using a cell-cycle nonspecific agent (BCNU) to maximize the number of actively proliferating cells and then expose these cells at the height of their growth to a cell-cycle specific agent (5-fluorouracil). Additionally, the scheduling minimizes the potential added toxicities of the two drugs. The difficulties inherent in the conduction of these Phase II Studies highlight the difficulties in predicting the usefulness of drugs for Phase III Studies from smaller studies conducted at single institutions.[22, 24]

Several studies have been undertaken to evaluate immunologic factors in brain tumors.[26] The underlying assumption of this work is that cancer cells can be distinguished from normal cells by the presence of distinctive antigens. However, despite the enormous literature that has centered on the question of tumor-specific antigens, the existence of such antigens remains speculative. More sophisticated immunologic studies are now in progress which aim to more clearly define and exploit suspected antigenic differences.

RADIATION NECROSIS

Recently, among patients enrolled in the Brain Tumor Study Group, there are some who are dying with progressive neurologic symptoms but without clear-cut radiologic or, rarely, pathologic evidence of mass effect or recurrent tumor. Thus, in one study, it was found that clinical symptoms might improve despite the presence of tumor on CT scan, or clinical symptoms might deteriorate in the absence of tumor.[6] Preliminary results of a CT scan study, part of BTSG 75–01, also revealed that while CT scan predicted clinical deterioration in some patients, it did not predict clinical deterioration in an almost equal number. The best explanation, at present, for such clinical deterioration in the absence of CT scan evidence of tumor recurrence or mass effect is radiation effect.

All patients undergoing surgery and radiotherapy develop ventricu-

lar dilatation (occasionally simulating hydrocephalus) as well as sulcal atrophy. Such loss in cerebral volume may be sufficient to preclude the development of mass effect. Additionally, the character of any remaining tumor may be so altered by radiotherapy (and chemotherapy) that it may become isodense (invisible) and/or not "enhance" on CT scan after administration of contrast material. In a recent study, radiation necrosis developed in 4 of 17 patients who had received 5000 to 6000 rads. There was a strong predilection for the white matter adjacent to the tumor with scant quantities of residual tumor and little mass effect.[5]

Radiation may result in two types of delayed reactions. The most common one consists of extensive coagulation necrosis with vascular thickening, perivascular exudation, petechiae, telangiectases, and perivascular chronic inflammatory cell infiltrates.[5, 23, 30, 35] The second and less common type consists of punched-out plaques of demyelination resembling multiple sclerosis with pronounced microglial and astrocytic proliferation. Associated blood vessels show few degenerative changes.[23, 25] The prominence of vascular changes in the majority of cases and the brunt of experimental evidence indicates that vascular changes are primary in the development of radiation necrosis.[30, 35]

CONCLUSION

Despite the progress in increasing both survival and quality of survival, it is painfully apparent that virtually all patients with malignant gliomas die of this disease. The major reason for death remains failure to eradicate the primary lesion. When a brain tumor develops, the tumor shares its space with the brain which occupies 1200 ml within the confines of the skull. In this space, 100 gm of tumor, equivalent to one hundred billion cells, is usually lethal. Patients presenting to a physician because of major symptoms usually have tumors 30 to 60 gm in size. Assuming an initial tumor burden of 100 gm, or one hundred billion cells, a subtotal surgical resection might remove 99 per cent of the tumor, leaving behind one gm or one billion cells (a two log kill). Radiation therapy might also achieve a two log kill and reduce the postoperative tumor burden to 0.01 gm or ten million cells. It would then be left to chemotherapy to further reduce the population of tumor cells to 0.0001 gm or 100 thousand cells, a size where the body's own natural immune mechanisms can kill the tumor. However, the surgeon is rarely able to do a complete resection; conventional radiation therapy falls short of the necessary two logs; and the chemotherapeutic agents currently available produce, at most, only a one log kill, thus permitting the tumor to grow at a rate faster than it can be killed.[41] Improved surgical techniques, including more complete resections aided by preoperative planning by CT scan, radiation therapy augmented by radiation sensitizers and suprafractionation, and improved chemotherapy and immunotherapy including new drugs with optimum combinations and schedules, may, in the near future, result in an even better rate of tumor kill.

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REFERENCES

1. Ambrose, J., Gooding, M. R., and Richardson, A. E.: An assessment of the accuracy of computerized transverse axial scanning (EMI scanner) in the diagnosis of intracranial tumor. Brain, *98*:569–582, 1975.
2. Bailey, P., and Bucy, P.: Oligodendrogliomas of the brain. J. Pathol. Bacteriol., *32*:735–751, 1929.
3. Bender, M., and Elizan, T.: The non-surgical management of brain tumors. Trans. Amer. Neurol. Assoc., *87*:20–24, 1962.
4. Bryant, P.: CSF seeding of intracranial tumours: a study of 96 cases. Clin. Radiol., *25*:355–360, 1974.
5. Burger, P. C., Mahaley, M. D., and Dudka, L.: The morphologic effects of radiation administered therapeutically for intracranial gliomas. Cancer (in press).
6. Carella, R. J., Pay, N., and Newall, J.: Computerized (axial) tomography in the serial study of cerebral tumors treated by radiation. Cancer, *37*:2719–2728, 1976.
7. Concannon, J. P., Kramer, S., and Berry, R.: The extent of intracranial gliomata at autopsy and its relationship to techniques used in radiation therapy of brain tumors. Amer. J. Roentgen., *84*:99–107, 1960.
8. Douglas, B. G.: Preliminary results using superfractionation in the treatment of glioblastoma multiforme. J. Canad. Assoc. Radiol., *28*:106–110, 1977.
9. Erlich, S. S., and Davis, R. L.: Spinal subarachnoid metastasis from primary intracranial glioblastoma multiforme. Cancer, *42*:2854–2864, 1978.
10. Feigin, I., and Budzilovich, G. N.: Tumors of neurons and their precursors. J. Neuropathol. Exp. Neurol., *39*:483–506, 1974.
11. Finkemeyer, H., Pfingst, E., and Zulch, K. J.: The astrocytomas of the cerebral hemisphere. *In* Vinken, P. J., and Bruyn, G. W., eds.: Handbook of Clinical Neurology, Vol. 18. Amsterdam, North Holland Publishing Company, 1975, pp. 1–47.
12. Fokes, E. C., and Earle, K. M.: Ependymomas: clinical and pathological aspects. J. Neurosurg., *30*:585–594, 1969.
13. Frankel, S. A., and German, W. J.: Glioblastoma multiforme. J. Neurosurg., *15*:489–503, 1958.
14. Gerstner, L., Jellinger, K., and Heiss, W. D.: Morphological changes in anaplastic gliomas treated with radiation and chemotherapy. Acta Neurochirg., *36*:117–138, 1977.
15. Hart, M. N., Petito, C. K., and Earle, K. M.: Mixed gliomas. Cancer, *33*:134–140, 1974.
16. Hitchcock, E., and Sato, F.: Treatment of malignant gliomata. J. Neurosurg., *21*:497–505, 1964.
17. Hoshino, T., Wilson, C. B., Rosenblum, M. L.: Chemotherapeutic implications of growth fraction and cell cycle time in glioblastomas. J. Neurosurg., *43*:127–135, 1975.
18. Janish, W., and Schreiber, D.: *In* Bigner, D., and Swenberg, J. eds.: Experimental Tumors of the Central Nervous System. Kalamazoo, Michigan, Upjohn Company, 1977, pp. 9–160.
19. Jellinger, K.: Glioblastoma multiforme. Morphology and Biology. Acta Neurochirg., *42*:5–32, 1978.
20. Jelsma, R., and Bucy, P.: The treatment of glioblastoma multiforme of the brain. J. Neurosurg., *27*:388–400, 1967.
21. Kricheff, I. I., Becker, M., and Schneck, S. A.: Intracranial ependymomas. Amer. J. Roentgen., *91*:167–175, 1964.
22. Kumar, A. R. V., Renaudin, J., and Wilson, C. B.: Procarbazine hydrochloride in the treatment of brain tumors. J. Neurosurg., *40*:365–371, 1974.
23. Lampert, P. W., and Davis, R. L.: Delayed effects of radiation on the human central nervous system. Neurology, *14*:912–917, 1964.
24. Levin, V. A., Freeman-Dove, M., and Landahl, H. D.: Permeability characteristics of brain adjacent to tumors in rats. Arch Neurol., *32*:785–791, 1975.
25. Lieberman, A., LeBrun, Y., and Glass, P.: Use of high dose corticosteroids in patients with inoperable brain tumors. J. Neurol. Neurosurg. Psychiatry, *40*:678–682, 1977.
26. Mahaley, M. S., Brooks, W. M., and Roszman, T. L.: Immunobiology of primary intracranial tumors. J. Neurosurg., *46*:467–476, 1977.
27. Marsa, G. W., Goffinet, D. R., and Rubinstein, L. J.: Megavoltage irradiation in the treatment of gliomas of the brain and spinal cord. Cancer, *36*:1681–1689, 1975.

28. Matsukado, Y., McCarty, C., and Kernohan, J. W.: The growth of glioblastoma multiforme (astrocytomas grades 3 and 4) in neurological practice. J. Neurosurg., *18*:636–644, 1961.
29. Morantz, R. A., Feigin, I., and Ransohoff, J.: Clinical and pathological study of 24 gliosarcomas. J. Neurosurg., *45*:398–408, 1976.
30. Nakagani, H., Brunhart, G., and Kemper, T. L.: Monkey brain damage from radiation in the therapeutic range. J. Neurosurg., *44*:3–11, 1976.
31. Polmeteer, F. E., and Kernohan, J. W.: Meningeal gliomatosis. Arch. Neurol. Psychiatry, *57*:593–616, 1947.
32. Ransohoff, J., and Lieberman, A.: Surgical therapy of primary malignant brain tumors. Clin. Neurosurg., *25*:403–411, 1978.
33. Reagan, T. J., Bisel, H. F., and Childs, D. S.: Controlled study of CCNU and radiation therapy in malignant astrocytoma. J. Neurosurg., *44*:186–190, 1976.
34. Roth, J. G., and Elvidge, A. R.: Glioblastoma multiforme: A clinical survey. J. Neurosurg., *17*:736–750, 1960.
35. Rottenberg, D. A., Chernik, N. L., and Deck, M. D.: Cerebral necrosis following radiotherapy of extracranial neoplasms. Ann. Neurol. *1*:339–357, 1977.
36. Russell, D. S., and Rubinstein, L. J.: *In* Pathology of Tumors of the Nervous System. Baltimore, Williams & Wilkins Co., 4th ed., pp. 147–282.
37. Salazar, O. M., Rubin, P., and McDonald, J. V.: Patterns of failure in intracranial astrocytomas after irradiation: Analysis of dose and field factors. Amer. J. Roentgen., *126*:279–292, 1976.
38. Schabel, F. M., Johnston, T. P., and McCaleb, G. S.: Experimental evaluation of potential anti-cancer agents. VIII. Effects of certain nitrosoureas on intracerebral L1210 Leukemia. Cancer Res., *23*:725–733, 1963.
39. Scherer, H. J.: The forms of growth in gliomas and their practical significance. Brain, *63*:1–35, 1940.
40. Schuster, H., Jellinger, K., Gund, A.: Extracranial metastases of anaplastic cerebral gliomas. Acta Neurochirg., *35*:247–259, 1976.
41. Shapiro, W.: Chemotherapy of nervous system neoplasms. *In* Primary Intracranial Neoplasms. *In* Scher, J., and Ford, D., eds.: New York, Spectrum Press, (in press).
42. Shapiro, W., Basler, G. A., and Chernik, N.: Human brain tumors transplanted into nude mice. J. Natnl. Cancer Inst. (in press).
43. Shaw, C. M., Sumi, S. M., and Alvord, E. C.: Fast neutron irradiation of glioblastoma multiforme. J. Neurosurg., *49*:1–12, 1978.
44. Sklanshy, B. D., Mann-Kaplan, R. S., and Reynolds, A. F.: 4′demethyl-epipodophyleotoxin-β,D-thenylidene-glucoside (PTG) in the treatment of malignant intracranial neoplasms. Cancer, *33*:460–467, 1974.
45. Smith, D. R., Hardman, J. M., and Earle, K. E.: Metastasizing neuroectodermal tumors of the central nervous system. J. Neurosurg., *31*:50–58, 1969.
46. Taveras, J., Thompson, H. G., and Pool, J. L.: Should we treat glioblastoma multiforme? Amer. J. Roentgen., *87*:473–479, 1962.
47. Urtasun, R., R., Band, P., and Shapman, J. D.: Radiation and high dose metronidazole in supratentorial glioblastoma. New Engl. J. Med., *294*:1364–1367, 1976.
48. Vick, N. A., Khandekar, J. D., and Bigner, D. D.: Chemotherapy of brain tumors. The "blood-brain barrier" is not a factor. Arch. Neurol., *34*:523–526, 1977.
49. Walker, M. D., Alexander, E., and Hunt, W. E.: Evaluation of mithramycin in the treatment of anaplastic gliomas. J. Neurosurg., *44*:655–667, 1976.
50. Walker, M. D., Alexander, E., and Hunt, W.: Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. J. Neurosurg., *49*:333–343, 1978.
51. Wasserman, T. H., Phillips, T. L., and Johnson, R. J.: Initial clinical and pharmacologic evaluation of misonidazole (RO–07–0582), a hypoxic cell radiosensitizer. Internat. J. Radiation Oncol. Biol. Physics, in press.
52. Weir, B., Band, P., and Urtasun, R.: Radiotherapy and CCNU in the treatment of high grade supratentorial astrocytomas. J. Neurosurg., *45*:129–133, 1976.
53. Willson, N., and Duffy, P. E.: Morphologic changes associated with combined BCNU and radiation therapy in glioblastoma multiforme. Neurology, *24*:465–471, 1974.
54. Zimmerman, H. M.: Brain tumors: their incidence and classification in man and their experimental production. Ann. N.Y. Acad. Sci., *159*:337–359, 1969.

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Advances in Diagnosis: Cranial and Spinal Computed Tomography

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In the last two years, refinements of medical interpretation, release of new contrast agents, and improvements in scanner technology for computed tomography (CT) have resulted in improved CT diagnosis and novel applications of CT to diagnostic problems. Fallacious concepts have been corrected; new developments appear to be nearing clinical application. The following discussion addresses these advances and assumes a basic knowledge of CT such as may be obtained in a variety of primers on computed tomography.[17, 20, 55, 62]

In addition the reader's attention is called to the report of Latchaw et al.[39] which provides a basic protocol for determining whether to employ routine non-enhanced CT and/or contrast-enhanced CT scans for particular clinical problems, and to the paper of Norman et al.[56] which discusses the optimal dosage of contrast agent for contrast-enhanced CT.

Technical Considerations — Three Dimensional Images

Initially, computed tomography was performed only in the axial plane. The serial images obtained were then displayed side by side for mental integration into a three dimensional representation of intracranial structures. However, normal anatomy and pathology are demonstrated best when the CT section passes perpendicularly through the area of interest. Thus, meningiomas, subdural hematomas, and other lesions of the orbital plate, floor of the temporal fossa, and high

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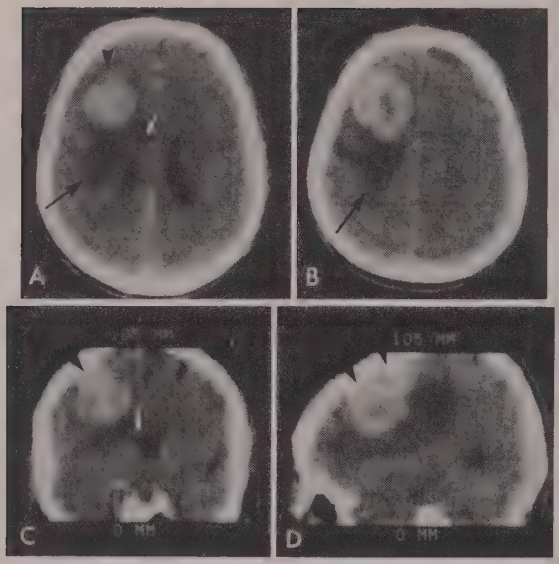

Figure 1. Computer-generated coronal and sagittal reconstructions from a 53 year old man with metastatic epidermoid carcinoma. Courtesy of Dr. Joseph Dooley, St. Louis, Missouri. *A* and *B*, CECT scans. Two images from the series of axial sections reveal compression of the left lateral ventricle (white arrow) by a large, intensely enhancing left posterior frontal mass (arrowhead), with significant surrounding lucent edema (black arrows). *C*, Coronal section CECT generated by the computer from the entire series of axial section CT scans. The mass (arrowhead) extends to the cortex and inner table, is associated with significant subjacent edema, and displaces the left frontal horn (white arrow) inferiorly and to the right. *D*, Sagittal section CECT generated by the computer from the series of axial section CECT scans. Anterior is to the reader's left. A large portion of the mass lies along the cerebral cortex (arrowheads). Nearly the entire deep surface is outlined by lucent cerebral edema. Sagittal and coronal reconstructions aid understanding of the exact relationship of a mass to all the important structures surrounding it.

convexity-parasagittal region are identified more readily and localized more accurately on coronal or sagittal CT scans, rather than on the customary axial CT scans. Such "right angle" coronal and sagittal CT sections have been achieved in two different ways:

DIRECT 90 DEGREE IMAGES. Coronal images may be obtained directly if the patient hyperextends his neck to bring the coronal plane parallel with the scanning plane.[21, 77] Most patients can manage to hyperextend the neck 30 to 45 degrees. If the patient is first placed on a board which can be elevated to a 45 degree inclination, then hyperextension of the neck an additional 45 degrees achieves a 90 degree rotation which permits direct coronal or near-coronal CT sections.[19] Sagittal images may be obtained directly if the patient's crown-rump length is small enough to fit into the scanning gantry (with legs straddling the sides of the scanner).[22] This method is now restricted to very small infants, in whom it has been used to scan the length of the spinal cord. If the scanning gantry has a very large opening, adult patients

can be placed on an extension table parallel to the scanner with one arm and shoulder through the hole and the neck and head in the hole nearly parallel to the gantry.[1]

COMPUTER-RECONSTRUCTED 90 DEGREE IMAGES. Coronal and sagittal images may be reconstructed in the computer from closely spaced axial images, provided that the patient does not move significantly during the entire time required to obtain the serial axial sections[41] (Fig. 1). If the patient has not moved, the computer can then stack the axial sections like a pile of coins and integrate along any given vertical slice to produce reconstructed sagittal and coronal sections. This method is the most desirable since only a single series of radiation exposures is required and the time for scanning is reduced. However, minor motion of the patient on even one of the multiple slices in the middle of the stack may degrade the entire reconstruction.

FUNCTIONAL ANATOMY OF THE CEREBRAL CORTEX

Improvements in scanner resolution and refinements of appreciation of anatomic detail now permit accurate identification of the main groupings of gyri and sulci along the medial and lateral surfaces of the cerebral cortex (Fig. 2*A*). In certain cases, the individual sulci and gyri

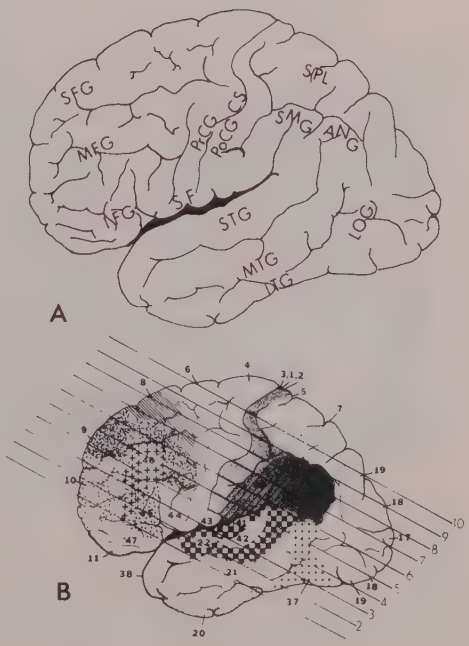

Figure 2. *Normal Anatomy of the Gyri and Brodmann Areas. Diagrams of the Lateral Surface of the Left Cerebrum. A,* Gyral anatomy of the cerebral cortex. The superior, middle and inferior frontal gyri are designated SFG, MFG and IFG respectively. The precentral gyrus, central sulcus, and postcentral gyrus are designated PrCG, CS and PoCG. The superior parietal lobule, supramarginal gyrus, angular gyrus and lateral occipital gyrus are designated SPL, SMG, ANG and LOG. The Sylvian fissure and the superior, middle and inferior temporal gyri are designated SF, STG, MTG and ITG. CT delineates these gyri well (Cf. Fig. 3). *B,* Brodmann areas (superimposed on the gyri delineated in *A*) Reference lines 1 to 10 correspond to the locations of serial CT sections oriented at the standard angle for CT scanning. The individual Brodmann areas are numbered. Those Brodmann areas crossed by each CT reference line are the cortical areas delineated in the corresponding CT sections. (Cf. Fig. 7). (*From* Gado, M., Hanaway, J., and Frank, R.: J. Comput. Assist. Tomogr., 3:1–19, 1979. Reproduced by permission.)

can be named precisely.[18, 23, 45, 49, 55] Gado, Hanaway and Frank have correlated this improved anatomic definition with the known loci of the Brodmann areas to produce a beautiful topographic display of the CT appearance of the Brodmann areas for correlation with symptoms.[18]

A CT section through the lower most portion of the ventricular system (Fig. 2, reference line 3) passes through the inferior frontal lobe, the Sylvian fissure, and the temporal lobe. It delineates the superior, middle, and inferior frontal gyri and the superior, middle, and inferior temporal gyri. In doing so, it depicts the anatomic loci of Brodmann areas 10, 46, 45, 44 and 6 along the lateral surface of the frontal lobe; areas 41, 42, and 22 along the lateral surface of the temporal lobe; and areas 37, 20, 36, 35, 28 and 34 along the inferomedial surface of the temporal lobe (Figs. 3 and 7). Similarly, a CT section through the upper portion of the lateral ventricles (Fig. 2, reference line 7) passes through the superior frontal lobe, central sulcus, anterior portion of the parietal lobe, the posterior portion of the Sylvian fissure, the posterosuperior temporal sulcus, the posterosuperior temporal lobe, and the occipital lobe. This section intersects the superior frontal, middle frontal and precentral gyri of the frontal lobe; the postcentral gyrus of the parietal lobe; the supramarginal and angular gyri which straddle the posterior Sylvian fissure and superior temporal sulcus respectively; and the lateral occipital gyrus, lingual gyrus, and calcarine cortex of the occipital lobe. This CT section displays Brodmann's areas 8, 6 and 4 along the lateral surface of the frontal lobe; 3, 1 and 2 along the

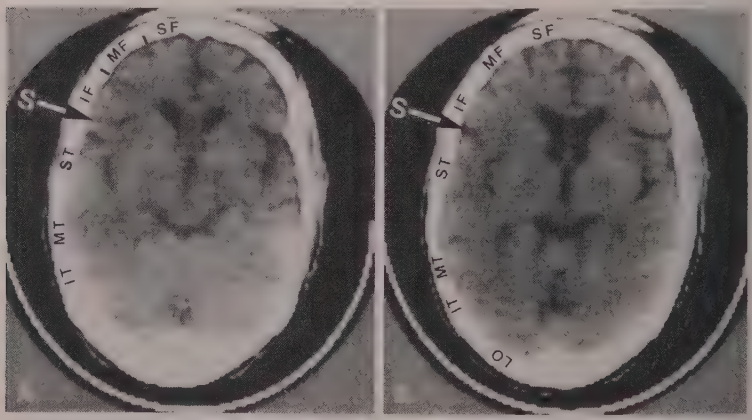

Figure 3. *Gyral Anatomy. A,* Non-contrast-enhanced CT scan along reference line 3 clearly delineates the superior frontal gyrus (SF), middle frontal gyrus (MF), inferior frontal gyrus (IF) and the Sylvian fissure (arrow S). Compare with the opposite side. The superior temporal (ST), middle temporal (MT) and inferior temporal (IT) gyri are less clearly defined but are known to occupy the regions indicated. *B,* Non-contrast-enhanced CT scan along the next higher reference line 4 demonstrates the consistent gyral identification possible by CT. LO indicates the lateral occipital gyrus. Gyral identification may be carried out on serial CT sections utilizing the reference guides, until all the major gyri of the cerebral hemisphere have been delineated.

anterior lateral surface of the parietal lobe; areas 40 and 39 along the supramarginal and angular gyri, and areas 19, 18, and 17 along the lateral and medial surface of the occipital lobe. Infarctions and other lesions in these regions therefore can now be correlated with the Brodmann areas affected. This analysis should permit a clearer understanding of the patient's signs and symptoms. It may also provide a research tool for refining understanding of the functional topography of the cortex.

CEREBRAL INFARCTION

A series of papers now provides some basic data on the CT appearance of cerebral infarction and the accuracy to be expected in detecting it.[5, 35, 63, 76, 79] *Non-contrast-enhanced computed tomography (NCT)*

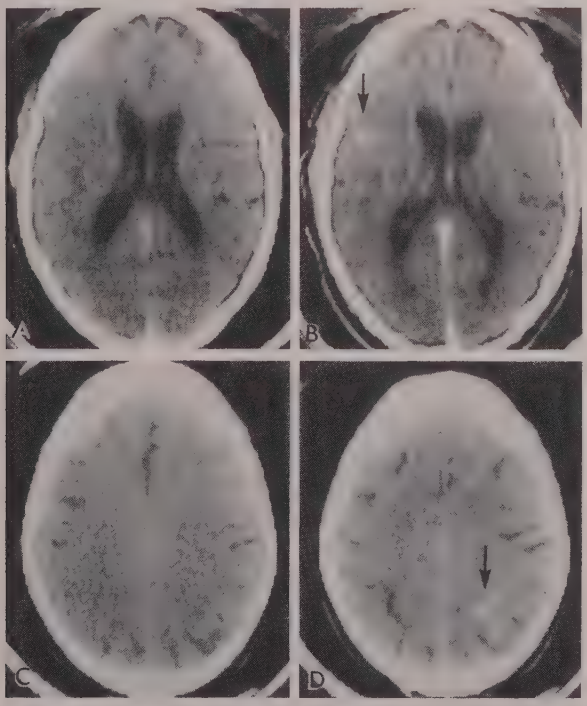

Figure 4. Cerebral ischemia and/or infarction revealed only with contrast enhancement. This 45 year old man had aortic insufficiency, dissecting hematomas of both common carotid arteries, and episodic transient ischemic attacks. *A*, Non-enhanced scan shows no abnormality. *B*, CECT scan performed at the same time reveals a small zone of contrast enhancement (arrow) corresponding to the ischemic zone. *C*, Non-enhanced scan 3 months later (higher level) reveals no abnormality. *D*, CECT scan reveals a small focus of contrast enhancement (arrow) corresponding to another ischemic zone.

detects 48 per cent of supratentorial ischemic infarctions on the day of ictus.[5] Sensitivity increases with time to a peak of 74 per cent at days 10 and 11, and declines thereafter, so only residual changes are observed in 60 per cent of patients after 1 month.[5] *Contrast-enhanced CT* (CECT) reveals an additional 11 per cent of ischemic infarctions not detected by NCT (Fig. 4), but partially obscures 5 per cent of low density infarctions seen initially on NCT.[5, 76] *Radionuclide scans* in the second week after ictus reveal 8 per cent of infarctions that are not seen by CT.[5] On the basis of a small number of cases, NCT appears to detect 37 per cent of infratentorial infarctions if performed as near to the ictus as possible, and 31 per cent of infratentorial infarctions if performed 7 to 10 days later.[5] Multiple areas of infarction are detected in 6.4 per cent of patients.[5]

If the CT appearance of infarction is considered in two temporal categories:[63]

IN THE PERIOD FROM 1 TO 7 DAYS: 20 per cent of infarctions appear isodense with normal brain (Fig. 4).

Approximately 70 per cent have low density areas with variably ill-defined or well-defined margins (Fig. 5).

Approximately 10 per cent of infarctions are at least partially hemorrhagic.

40 per cent of the lesions correspond to a vascular distribution or show the typical wedge shape (Fig. 5). Sixty per cent, particularly deep infarctions, are ovoid or round with a less easily discerned vascular distribution (Fig. 6).

25 per cent show obvious blush on CECT; 25 per cent show faint blush on CECT, and 45 to 50 per cent show no discernible blush on CECT (Figs. 4 and 7).

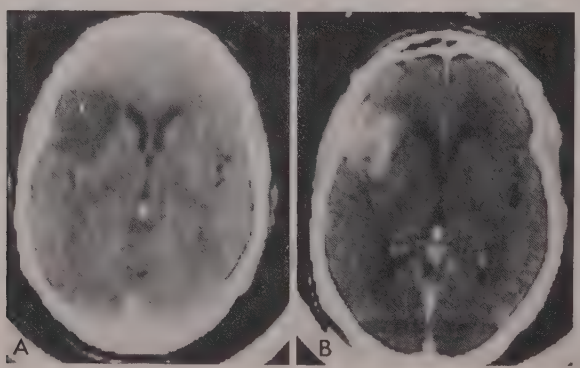

Figure 5. Wedge-shaped cerebral infarction with delayed appearance of gyral blush in a 68 year old man. *A*, CECT on the day of ictus reveals a wedge-shaped zone of decreased density in the anterior division of the left middle cerebral artery distribution. Faint linear blush (white arrowhead) is present in the lucency. No mass effect is present. *B*, CECT at the same level 16 days later shows marked gyral blush in nearly the entire region of lucency.

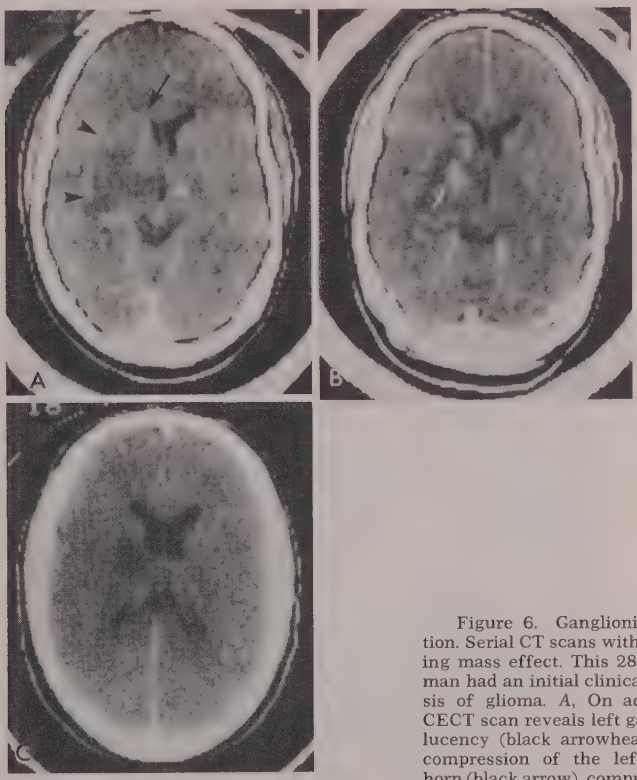

Figure 6. Ganglionic infarction. Serial CT scans with decreasing mass effect. This 28 year old man had an initial clinical diagnosis of glioma. *A*, On admission, CECT scan reveals left ganglionic lucency (black arrowheads) with compression of the left frontal horn (black arrow), compression of the third ventricle (white arrowhead), and left to right midline shift. There is no contrast enhancement. (Compare with Figure 9, a ganglionic astrocytoma.) *B*, CECT 32 days later reveals contrast enhancement (white arrow) and very slightly diminished mass effect. Although each of these CT scans would suggest a diagnosis of neoplasm, the reduction in mass effect warranted an additional delay in pursuing aggressive antineoplastic therapy. *C*, CECT 13 days after *B*. The significant reduction in both mass effect and contrast enhancement in a patient not receiving corticosteroids strongly suggests a diagnosis of infarction. Although this section is not exactly comparable, review of the entire series of sections left no doubt as to the decreased mass effect.

Ischemic blush is frequently "gyral" (Figs. 5 and 7), but may assume any configuration. The specific pattern does not appear to correlate with size, shape, location or age of the infarction.[76] It has been suggested, however, that *purely* gyral blush, in patients with normal non-contrast-enhanced CT scans, indicates ischemic breakdown of the blood-brain barrier in viable tissue, and as such carries an excellent prognosis.[35]

Twenty to 25 per cent of infarctions exhibit mass effect of variable degree (Fig. 6). Patients in coma usually show the greatest mass effect.[35] A mass effect may be absent in the first few hours, and become

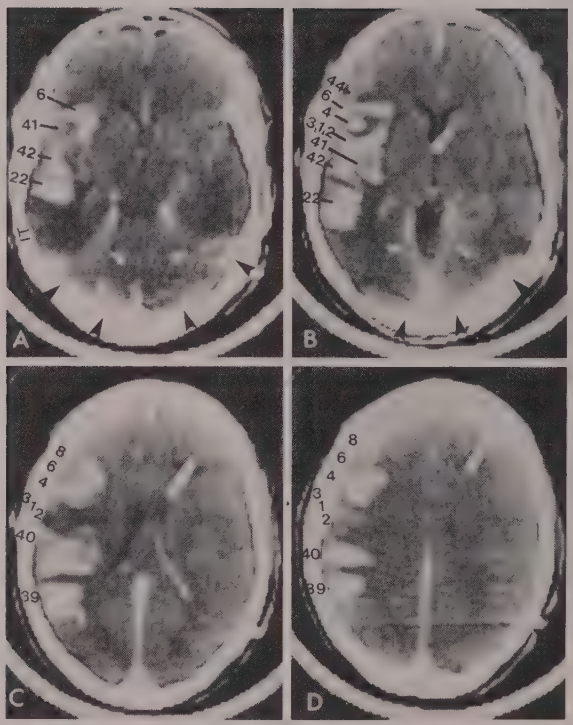

Figure 7. Infarction of the left cerebrum. CT localization to specific Brodmann areas. CECT scans in a 40 year old woman with severe left middle cerebral artery spasm and prolongation of the left arteriovenous circulation time to 10.0 seconds after subarachnoid hemorrhage, clipping of a left posterior communicating artery aneurysm, and insertion of a ventriculoperitoneal shunt for hydrocephalus. The gyral blush associated with the cerebral ischemia delineates the gyral anatomy corresponding to the Brodmann areas (see Figs. 2*B* and 3). *A*, CECT scan along reference line 3 reveals gyral contrast enhancement in Brodmann areas 6, 41, 42, and 22 with edema involving the inferior temporal gyrus (IT). Brodmann areas 10, 46, 45, and 44 are spared at this level. The white arrowheads indicate the tentorial blush and the black arrowheads the transverse dural sinuses which should not be mistaken for gyral blush. *B*, CECT scan along reference line 4 reveals gyral contrast enhancement in Brodmann areas 44, 6, 4, 3, 1, 2, 41, 42, and 22 (white and black arrowheads as in *A*). *C*, CECT scan along reference line 6 reveals gyral blush in Brodmann areas 8, 6, 4, 40, and 39. Areas 3, 1, and 2 appear to be spared at this level. *D*, CECT scan along reference line 7 reveals gyral blush in Brodmann areas 8, 6, 4, 40, and 39, but not 3, 1, and 2.

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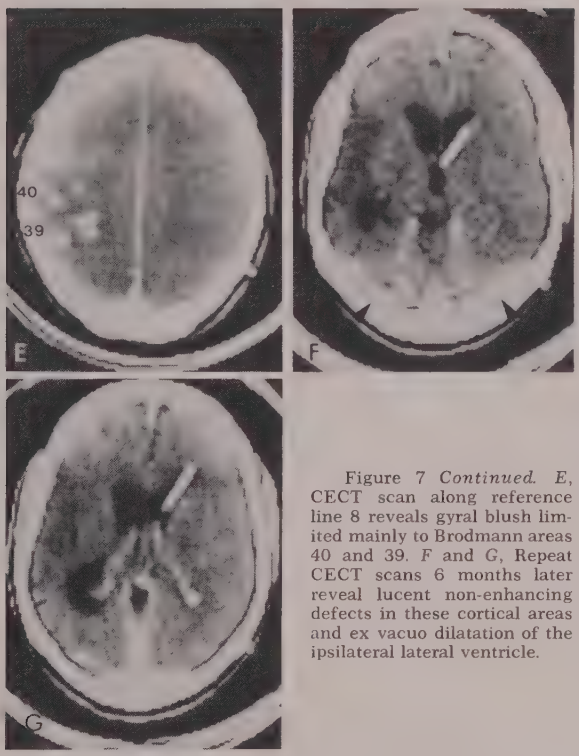

Figure 7 *Continued.* *E*, CECT scan along reference line 8 reveals gyral blush limited mainly to Brodmann areas 40 and 39. *F* and *G*, Repeat CECT scans 6 months later reveal lucent non-enhancing defects in these cortical areas and ex vacuo dilatation of the ipsilateral lateral ventricle.

gross at 48 hours or later.[35] If infarctions with mass effect are scanned sequentially, soon after ictus and again at 7 to 10 days, then over the 7 to 10 day period some 12 per cent show interval appearance of mass, 9 per cent show increased size of previously detected mass, 48 per cent show no change in the size of mass, and 30 per cent show decreasing size of mass. Campbell et al.[5] found that mass effect did not persist beyond 25 days in any patient.

IN THE PERIOD FROM 7 TO 28 DAYS: 30 per cent of infarctions appear isodense with normal brain.

3 per cent show identifiable hemorrhage.

30 per cent correspond to a vascular distribution.

7 to 10 per cent show a mass effect.

57 per cent show *ex-vacuo* dilatation of the adjacent ventricle[76] (Figs. 7F and 7G), and 60 to 70 per cent show contrast enhancement.

Interestingly, 6.5 per cent of patients scanned sequentially show positive NCT scans soon after the ictus and negative NCT scans at 7 to 10 days.[5] Conversely, 12.3 per cent of patients with a negative CT scan soon after ictus have a positive scan at 7 to 10 days.[5]

INFARCTION VERSUS TUMOR

Generally, an infarction appears as a zone of decreased density with little to no associated mass (Fig. 5A), whereas a neoplasm appears as a zone of decreased density with significant associated mass (Figs. 8 and 9). The decreased density of infarctions may be patchy or homogeneous, whereas the decreased density of neoplasms often appears to surround a focal mass. Many exceptions to these rules may make it very difficult to distinguish infarction from neoplasm in a given case.

At times CT fails to demonstrate any sign of existing pathology (Figures 4*A*, 4*C*, 8*A*, and 8*B*). Infarctions may be isodense rather than lucent (Fig. 4) and may show significant mass effect (Fig. 6) that increases in degree for a short time. Infarctions may exhibit any type and degree of contrast enhancement, or none at all. Neoplasms may be undetectable at the time of clinical presentation and become obvious only on sequential CT scans (Fig. 8). They may appear as zones of decreased density without mass effect (Fig. 9), or as lucent masses with little or no progression over time (Fig. 9). They too may show variable or absent contrast enhancement.

Computed tomography attempts to differentiate infarction from neoplasm on the basis of the initial CT images and the change in the CT appearance with time. In patients with infarctions, serial CT scans over 4 to 6 weeks document decrease in the degree of any associated mass. The mass effect may increase, or even appear for the first time, during the first 10 days after ictus, but will then show progressive decrease with time and will usually disappear completely by 25 days (barring second insult) (Fig. 6). In patients with infarction, the contrast enhancement will often have a "gyral" component (Figs. 5 and

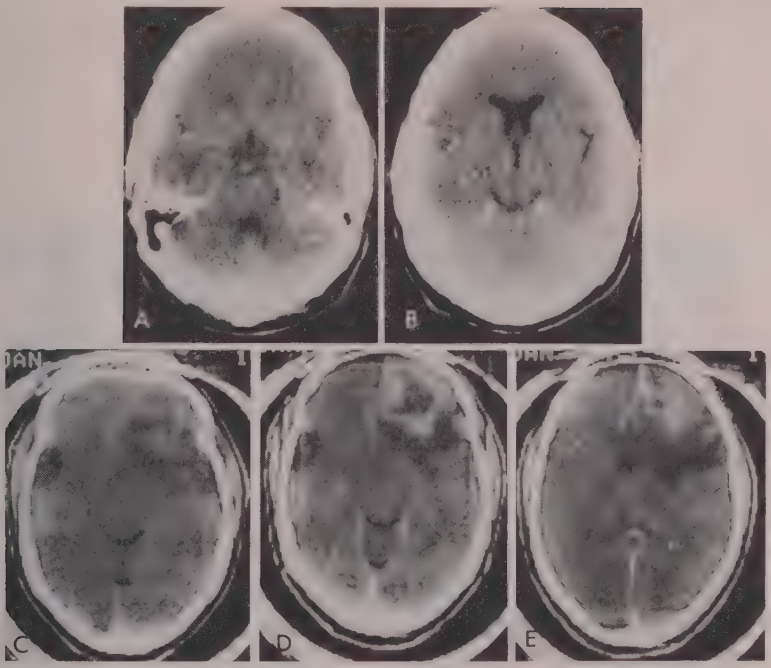

Figure 8. Glioblastoma multiforme. *A* and *B*, CECT scans are normal when this 57 year old man first presented with a seizure. *C*, Non-contrast-enhanced CT scan 6 months later reveals a large low right frontal mass with mixed attenuation. *D* and *E*, CECT scans now demonstrate a ring blush with surrounding edema and significant mass effect.

7). The blush of infarction will often appear or will increase in intensity during the 10 to 30 days post-ictus, and will then fade progressively (Fig. 5). Neoplasms usually increase the degree of mass effect and degree of enchancement with time unless the patient receives corticosteroid therapy or other forms of brain volume control (Fig. 9).

We believe that any patient with an equivocal clinical picture or an equivocal CT scan should have serial CT scans to help establish the diagnosis. The presence of gyral enhancement on the initial contrast-enhanced CT scan increases the liklihood of infarction. In such cases we temporize for 10 to 14 days and repeat the CT scan prior to performing invasive diagnostic tests or therapy. If the patient has not been placed on corticosteroid therapy or other agents to effect volume reduction, then an interval decrease in mass effect and degree of enhancement support the diagnosis of infarction (Fig. 6). Utilizing this approach, patients with equivocal or frankly misleading clinical presentations may be spared craniotomy and/or radiotherapy.

Gyral enhancement is not specific for infarction. It may be seen in such "hyperemic" states as arteriovenous malformations and post-

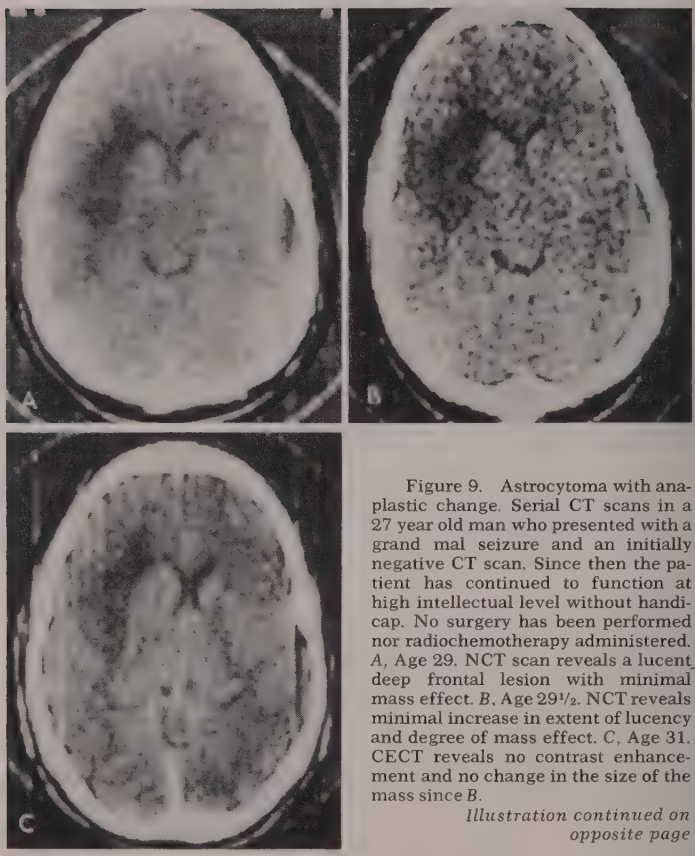

Figure 9. Astrocytoma with anaplastic change. Serial CT scans in a 27 year old man who presented with a grand mal seizure and an initially negative CT scan. Since then the patient has continued to function at high intellectual level without handicap. No surgery has been performed nor radiochemotherapy administered. *A*, Age 29. NCT scan reveals a lucent deep frontal lesion with minimal mass effect. *B*, Age 29½. NCT reveals minimal increase in extent of lucency and degree of mass effect. *C*, Age 31. CECT reveals no contrast enhancement and no change in the size of the mass since *B*.

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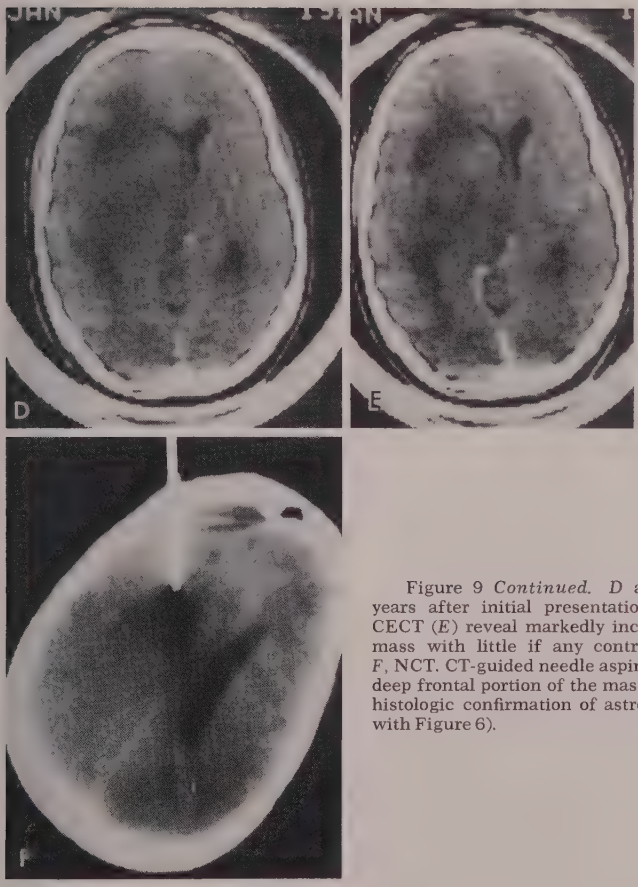

Figure 9 *Continued.* *D* and *E*, Age 33, 6 years after initial presentation. NCT (*D*), and CECT (*E*) reveal markedly increased size of the mass with little if any contrast enhancement. *F*, NCT. CT-guided needle aspiration biopsy of the deep frontal portion of the mass provided the sole histologic confirmation of astrocytoma (compare with Figure 6).

seizure status, and also within compressed normal brain surrounding a mass. Density simulating a gyral blush may be caused by subarachnoid hemorrhage in the sulci as well as by the pial-arachnoidal blush associated with meningitis, leptomeningeal carcinomatosis, implants of intracranial tumors, and meningeal irritation after subarachnoid hemorrhage.[15, 16, 47] Less frequently, extension of lucent edema into the white matter of multiple adjacent gyri simulates enhancement of the intervening gray matter.

DIAGNOSTIC PITFALLS AVOIDED

The work of many authors has contributed to improved understanding of the CT scan and has corrected many errors of appreciation.

Ring Blush

The appearance of a "ring blush" on CECT is a nonspecific indication of pathology (Fig. 10). The presence, absence, thickness, raggedness, size, degree of enhancement, and other characteristics of the ring appear useless for differential diagnosis. Although ring blush is seen most frequently with gliomas (Figs. 8C, 10A, 10B, and 11), metastases (Fig. 1B), and abscesses (Figs. 25, 10K, and 10L), it may also be observed in some patients with aneurysm, infarction, hematoma (Figs. 10C–10F), radiation necrosis[44] (Fig. 10J), a variety of benign tumors such as acoustic neuromas[50] and craniopharyngiomas, and at the site of previous intracranial surgery for diverse lesions (Fig. 10I). It seems certain that "ring blushes" will come to be described in at least some patients with most forms of neuropathology. Some specific comments appear warranted:

The ring blush appears to be a normal stage in the evolution of hematomas, appearing 3 days to 84 days after the initial bleeding and fading thereafter.[37, 82] Such a ring is usually seen when the hemorrhage is nearly isodense or already lucent and when the mass effect of the hematoma has diminished significantly. Initially the ring blush most probably represents breakdown of the blood-brain barrier, since it can be made to disappear with corticosteroid therapy.[37] Later the ring blush appears to represent enhancement in granulation tissue, and persists despite administration of steroids.[37] CT detection of a ring blush in a patient with an evolving *post-traumatic* hematoma does not necessarily indicate supervening abscess from an indriven foreign body or other pathology. Similarly CT detection of a ring blush in a patient with *spontaneous* hemorrhage should not necessarily be considered to be evidence of the underlying lesion responsible for the hemorrhage. Rather, in the absence of strong clinical indications to the contrary, and in the absence of CT evidence of increasing mass, ring blush in such patients may be followed to resolution by serial CECT scans.

In patients who have undergone intracranial resections, the operative bed may exhibit contrast enhancement for a variable period of

time, and then fade. Therefore appearance of a ring blush at the resection site does not necessarily indicate recurrent tumor, complicating abscess, or other abnormality. In the absence of CT evidence of increasing mass or strong clinical indication to the contrary, such ring blushes may also be followed to resolution with serial CECT scans.

In patients with brain abscess, the ring blush appears to correlate with the presence of a well-defined abscess capsule. The abscess ring and capsule are often thickest on their superficial surfaces and thinnest on their deep surfaces, perhaps explaining why abscesses frequently point toward and rupture into the ventricles.[81] In patients with infection, serial CT scans may demonstrate capsule formation and thinning of the deep capsular walls, thereby influencing the timing of surgical intervention. Ring blush with "daughter" rings, and gas bubbles trapped within the ring blush strongly suggest that the lesion is an abscess (Figs. 10*K*, 10*L*, 25). The mortality associated with brain abscess has decreased markedly as a result of (1) CT demonstration of the presence, site(s), and number of abscesses; (2) CT documentation of capsule formation and/or impending capsular rupture as a guide to timing of operative intervention; and (3) the success of CT-guided aspiration of abscesses.[48,68]

Cystic Versus Solid Tumors

CT does not distinguish effectively between cystic and solid tumors. Regions of tumor which are well defined, sharply marginated, homogeneously lucent, and appear "cystic" on CT may prove to be solid at surgery (Fig. 11).[38] Many of these cyst-like tumors are microcystic astrocytomas, but some are simply low density solid masses. Homogeneously lucent masses like epidermoid tumors may also appear cyst-like on CT and have density measurements very similar to those of cerebrospinal fluid.

On contrast-enhanced CT (CECT), tumor blush often defines an apparently hollow, spherical or multilobulated mass with walls which are ragged and inhomogeneous in thickness (ring blush). Although these hollows resemble central necrosis, this ring-like appearance may also be seen with solid tumors (Fig. 11*C and F*). Apparently solid tumor may be composed of several different perfusion compartments. CECT scans at the usual 5 to 30 minutes after infusion of contrast medium depict the leakage of contrast into some but not necessarily all of these perfusion compartments. Those yet unperfused may appear as holes. In such cases, serial CT scans over several hours may show complete opacification of the lesion.

In some cystic lesions, serial CT scans demonstrate layering of the dense contrast agent in the dependent portion of the cystic cavity. Only the presence of such a contrast-fluid level within the low density center of the tumor indicates reliably the presence of cyst within the tumor (Fig. 11*G*).[34, 43, 56]

Aneurysm Versus Tumor

CT can identify an aneurysm reliably when there is clear-cut luminal blush in close relationship to the parent vessel, laminated mural

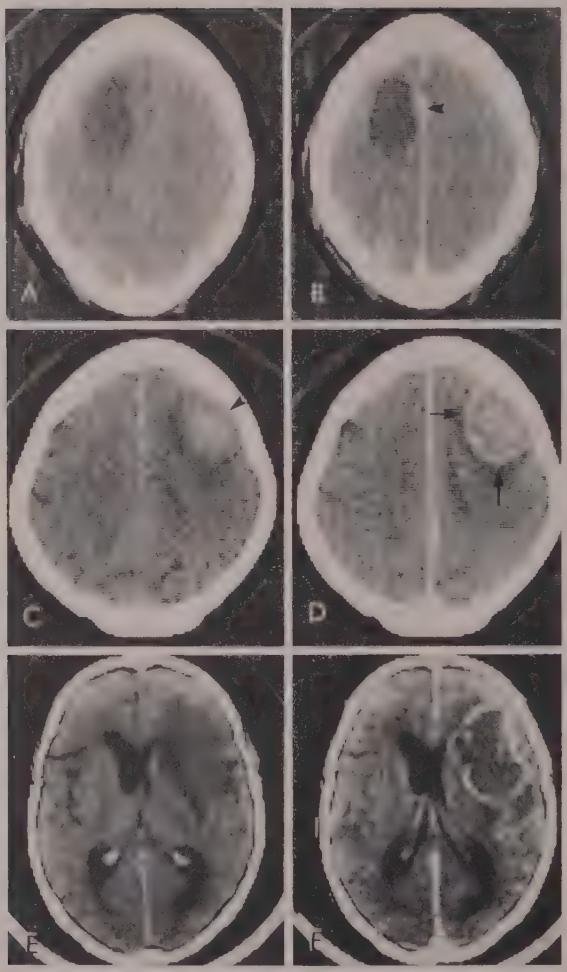

Figure 10. Ring Blush of Diverse Etiologies. Compare figures 8*D*, 11 and 24*A*. *A* and *B*. Astrocytoma. *A*, NCT reveals a homogeneously lucent mass. *B*, CECT shows a thin nearly even ring blush with slight thickening medially (arrowhead) along the falx. *C* and *D*. Dense hematoma in a 66 year old woman with thrombosed arteriovenous malformation. *C*, NCT 2 weeks after an acute hemorrhage reveals diminished density in the aging hematoma (arrowhead), surrounding lucent edema, and no significant mass effect. *D*, CECT reveals a slightly thick ring blush (arrows) circumscribing the hematoma. The ring blush of hematoma is usually situated exactly at the edge of the hemorrhage. *E* and *F*. Resolving lucent hematoma in a 73 year old man with known carcinoma of the prostate and pelvic lymph node metastases. *E*, NCT reveals a large lucent mass and midline shift. *F*, CECT shows a thin lobulated ring blush. Surgery, pathology and serial follow-up CT scans revealed no evidence of neoplasm.

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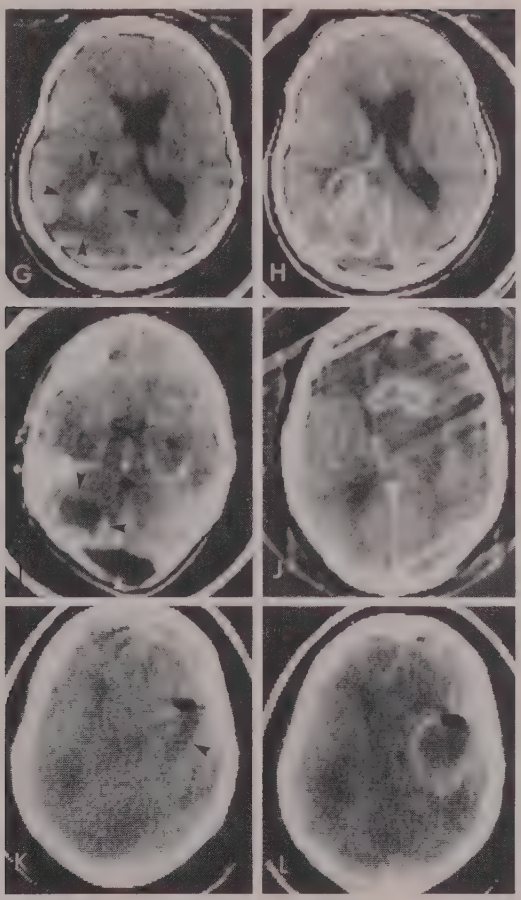

Figure 10 *Continued.* *G* and *H*, Hemorrhage into an astrocytoma after open biopsy and cyst decompression (not CT-guided). *G*, NCT reveals compression of the left atrium and occipital horn by a lucent left parieto-occipital mass (arrowheads) with central hemorrhage. *H*, CECT reveals a ring blush far larger than the hemorrhage itself. The discrepancy in size between the hemorrhage and the ring blush suggest that this is not a simple hematoma (Cf D. above). *I*, Operative bed. 46 year old woman 2 weeks after resection of left cerebellar ependymoma. CECT reveals a ring blush of irregular thickness (black arrowheads), lesser displacement of the fourth ventricle than seen on previous CT scans (white arrow), and a pseudomeningocele (white arrowhead). *J*, Radiation Necrosis. 66 year old woman with carcinoma of the right maxillary sinus, status post 6700 to 7100 rads to the right frontal lobe. CECT reveals a ring blush in the right frontal lobe with surrounding fronto-ganglionic lucency and marked midline shift. *K* and *L*, Gas abscess. 47 year old woman. Case courtesy James Naidich, M.D., and Roger Hyman, M.D., Manhasset, New York. *K*, NCT reveals marked ventricular compression and a focal collection of air (white arrow) superior to a lucent mass (arrowhead). *L*, CECT demonstrates a ring blush circumscribing the air and the mass. This air moved freely in the abscess cavity with changing patient position (compare with Figure 25, a multilocular abscess).

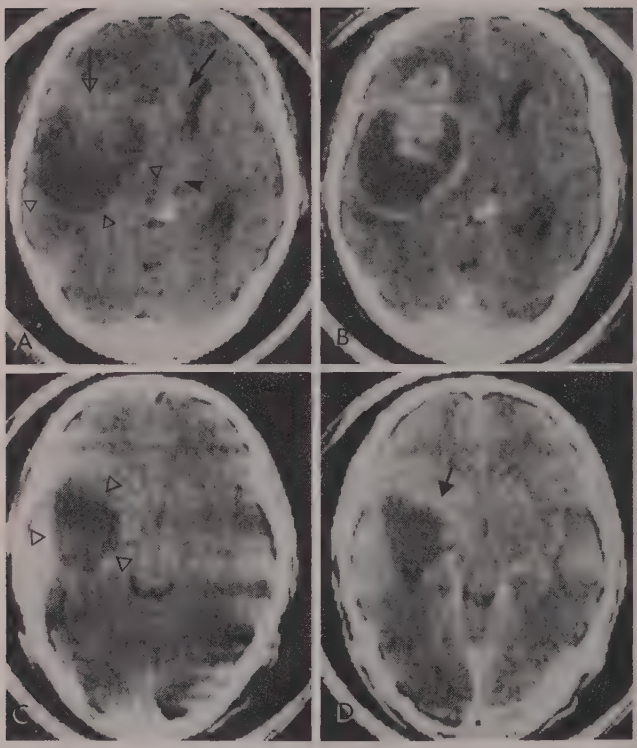

Figure 11. *Cystic versus Solid Tumor. A* and *B*, Cystic astrocytoma of the left temporal lobe in a 65 year old man.

A, NCT. The left frontal horn (black arrow), third ventricle (black arrowhead) and calcified pineal gland are displaced across the midline by a large left temporal mass composed of an isodense portion (open arrow) and a very well-defined lucent cyst (arrowheads). *B*, CECT reveals dense blush in the solid portion of the tumor and in the cyst wall.

C and *D*, Solid astrocytoma of the left temporal lobe in a 31 year old man.

C, NCT reveals a well-defined, homogeneously lucent, left temporal mass (white arrowheads). *D*, CECT reveals no contrast enhancement within or adjacent to the mass. The left middle cerebral artery (black arrow) is displaced anteromedially. Pathology revealed a microcystic astrocytoma.

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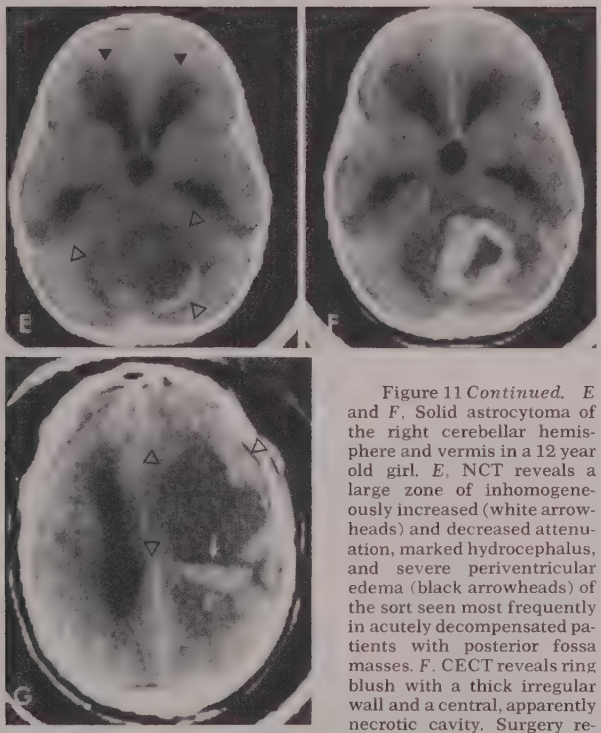

Figure 11 *Continued.* *E* and *F*, Solid astrocytoma of the right cerebellar hemisphere and vermis in a 12 year old girl. *E*, NCT reveals a large zone of inhomogeneously increased (white arrowheads) and decreased attenuation, marked hydrocephalus, and severe periventricular edema (black arrowheads) of the sort seen most frequently in acutely decompensated patients with posterior fossa masses. *F*, CECT reveals ring blush with a thick irregular wall and a central, apparently necrotic cavity. Surgery revealed only solid tissue with no evidence of any cystic or necrotic space. *G*, Cystic glioma in a 62 year old man. CECT reveals a fluid-contrast level (white arrow) layering in the dependent portion of a round, well-defined lucency (white arrowheads) proving that the lucency represents a large cystic space.

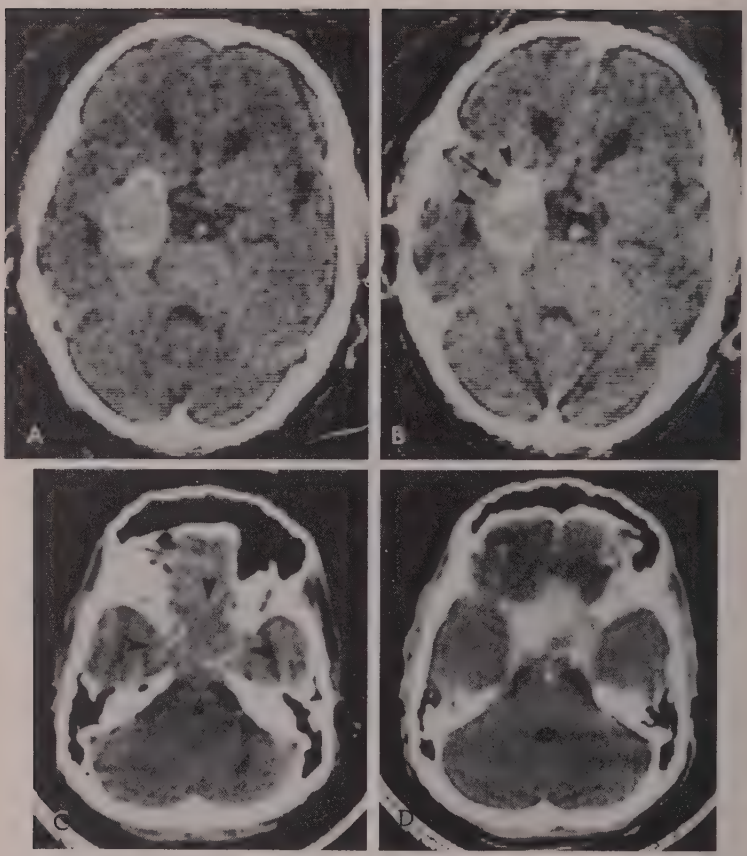

Figure 12. *Aneurysm Versus Tumor. A* and *B*. Typical giant aneurysm in a 51 year old man. *A*. NCT reveals a mass with an incomplete calcific rim and a homogeneous slightly dense center. *B*. CECT demonstrates a small luminal blush (arrow). Since the *dome* of the aneurysm frequently calcifies, the luminal blush most often lies adjacent to a discontinuity in the calcific ring (arrowheads). The soft tissue density between the calcific ring and the luminal blush is mural thrombus.

C, D, E. Giant post-traumatic aneurysm in a 28 year old man with a nasopharyngeal mass. *C*. NCT reveals massive destruction of the sella turcica and planum sphenoidale by a large nearly isodense, noncalcified mass (arrowheads) (see Figure 14). *D*. CECT shows homogeneous enhancement in much but not all of the mass. The blush is not particularly intense nor obviously "intraluminal" in nature.

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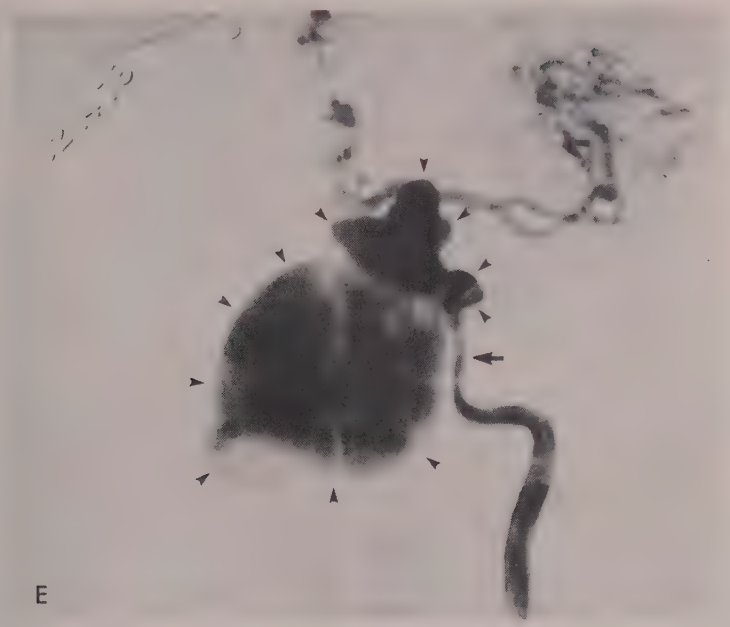

Figure 12 *Continued.* *E*, Angiogram performed prior to contemplated transnasal biopsy reveals a multilobulated giant aneurysm (arrowheads) which compresses the left internal carotid artery (arrow).

thrombus, rim calcification, and/or a peripheral ring blush which is probably related to granulation tissue on the external surface of the aneurysm (Figs. 12A and 12B). However, aneurysms may also appear "atypical" with nearly homogeneous density and nearly homogeneous contrast enhancement indistinguishable from that of tumor[51](Figs 12*C* and 12*D*). For this reason, CT cannot be used to *rule out* an aneurysm. Arteriography is still necessary to rule out an aneurysm prior to undertaking resection of a "tumor", especially when utilizing a limited surgical exposure such as a transsphenoidal approach to "pituitary adenoma" with small suprasellar extension.

Acute Hematomas

Most acute intracranial hemorrhages exhibit homogeneous, increased density.[3] However, some do appear to be inhomogeneous and some are homogeneously lucent. The density of blood appears to depend upon the concentration of hemoglobin protein.[54] In patients with normal hematocrits and normal hemoglobin protein, acute intracerebral hematomas are usually dense, and usually appear nearly homogeneously white. However, in patients with low hematocrits, acute hematomas may be expected to appear isodense or lucent. Kasdon et al. report a patient with a surgically and necropsy proven acute intracere-

bellar hematoma (5 cm in diameter) which appeared homogeneously lucent within 24 hours after ictus.[31] The hematocrit in that patient was 20 per cent. Zones of platelet clot, areas of admixture with cerebrospinal fluid (traumatic clots) and possibly positional gravitational density gradients may make a hematoma *in*homogeneous in density.

Pseudoatrophy

CT signs of cerebral "atrophy" should not be interpreted to mean irreversible loss of brain substance with poor prognosis. A number of investigators have shown that patients with psychogenic starvation, anorexia nervosa, kwashiorkor, and endogenous or exogenous Cushing's syndrome may exhibit CT signs of "atrophy" that disappear upon treatment of the underlying process.[2, 12–14, 24, 46] Serial CT scans in these patients show moderate dilatation of the lateral and third ventricles and/or prominent subarachnoid cisterns which diminish in size or revert to normal as the patient responds to therapy. The mechanisms underlying this phenomenon are uncertain and may well be different in the different diseases. Patients with malnutrition and low plasma proteins may pool fluid in the ventricles and sulci causing them to dilate. With treatment and rising plasma protein levels, the fluid could be returned to the intravascular space and/or excreted with reduction in ventricular and sulcal size.[24] Conversely in patients with Cushing's syndrome, the enlarged ventricles and sulci may represent a reduction in brain volume as a result of the dehydrating effect of the steroids. The reduction in ventricular and sulcal size may then represent return of brain water volume to normal after removal of excess steroids.[2]

It has also been suggested that the enlargement of the cerebrospinal fluid spaces could represent reduction in brain volume as a result of loss of brain substance. In kwashiorkor, the neurons of the gray matter are reduced in number and the remaining cells have swollen cytoplasm. These neuropathologic changes are reversible to a degree, depending on the age of onset and the duration of malnutrition.[12]

Patients with communicating hydrocephalus and high convexity–parasagittal obstruction and patients with subdural effusions may also exhibit dilatation of the ventricles and subarachnoid spaces similar to that seen with atrophy.[59] These should not be confused with atrophy.

Subarachnoid Hemorrhage

CT does not detect all acute subarachnoid hemorrhages. As is to be expected a priori, the detection rate must vary with the site and extent of bleeding (cerebrospinal fluid hematocrit). Although some published reports have indicated 100 per cent accuracy in detecting subarachnoid hemorrhage,[71] we have not found this to be true in our patient population.[47] A review of our series of patients with documented subarachnoid hemorrhage reveals that only 85 per cent of patients show CT evidence of subarachnoid hemorrhage in the first 48 hours after bleed; only 75 per cent show hemorrhage on CT scans in the period from 3 to 5 days after hemorrhage. The accuracy of detecting subarachnoid hemorrhage decreases markedly thereafter and reaches 29

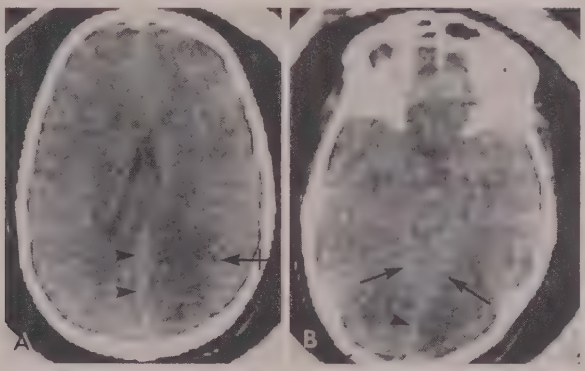

Figure 13. Subarachnoid hemorrhage in a 16 year old boy with bi-occipital contusion, more severe on the right. *A*, NCT. The line of increased density (arrowhead) corresponds to blood pooled in the posterior half of the interhemispheric fissure. *B*, NCT. The Y-shaped density corresponds to blood pooled on the tentorium (arrows) and in the interhemispheric fissure.

per cent 21 days after hemorrhage. We have also experienced great difficulty in distinguishing the linear density of interhemispheric subarachnoid hemorrhage from the thin linear density of a faintly calcified falx, and the thin linear density of a normal falx flanked by edematous, lucent occipital lobes (Fig. 13). We now regard increased density of the posterior half of the interhemispheric fissure as a treacherous sign of subarachnoid hemorrhage, to be used only with caution. It is a very important clue to *possible* subarachnoid hemorrhage, but is not itself diagnostic unless accompanied by other signs of hemorrhage.

METRIZAMIDE CT SCANNING

Metrizamide* is a non-ionic, non-dissociable, water-soluble contrast agent with relatively low lipid-solubility and relatively low neurotoxicity, which has recently been released for use in adults and children over age 12 years. Intrathecal administration of a low dose of metrizamide in isotonic form (4 to 7 ml of 190 mg I per ml) by lumbar puncture provides excellent opacification of the entire spinal and cranial subarachnoid space. With appropriate technique, the principal side effects are mild and transient, rarely lasting more than 12 hours. employed in patients receiving phenothiazines and should be used cautiously in patients with a past history of seizures.

These include headache (40 per cent), nausea (40 per cent), vomiting (36 per cent), and subtle perceptual aberrations (12 per cent). Many patients experience no side effects (36 per cent).[8] Seizures have been reported rarely, usually in patients receiving higher doses of metrizamide or neuroleptic medication. Metrizamide should, therefore, not be

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The ability to opacify the subarachnoid space with metrizamide permits CT to be utilized in a variety of new ways.

Extra-Axial Masses

Metrizamide computed tomography defines extra-axial intracisternal tumors more accurately than conventional CT in some cases.[7, 9, 67] Most tumors lying in the cerebrospinal fluid can be detected by conventional CT, because they have densities different from cerebrospinal fluid or because they show tumor blush.[51] However, isodense, nonenhancing masses such as arachnoid cysts, epidermoid tumors, some craniopharyngiomas, some suprasellar components of pituitary adenomas and some exophytic astrocytomas, may be very difficult or impossible to detect by conventional CT. In the past, these often required pneumography for definition. When metrizamide opacifies the CSF, masses which were isodense with cerebrospinal fluid suddenly appear as lucent filling defects in the densely opacified cerebrospinal fluid and are readily detected (Fig. 14). CT identification of a thin line of opaci-

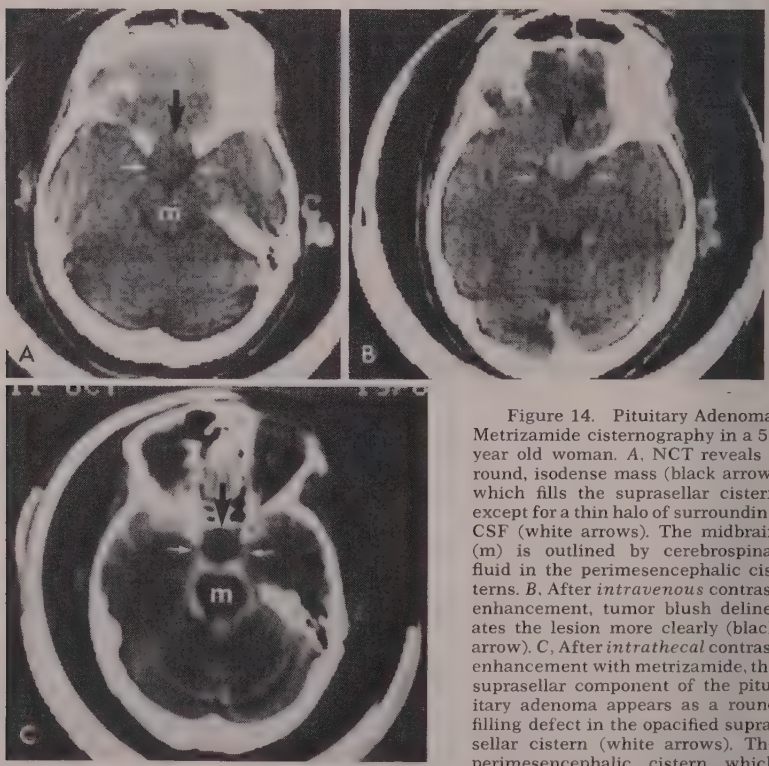

Figure 14. Pituitary Adenoma. Metrizamide cisternography in a 55 year old woman. *A*, NCT reveals a round, isodense mass (black arrow) which fills the suprasellar cistern except for a thin halo of surrounding CSF (white arrows). The midbrain (m) is outlined by cerebrospinal fluid in the perimesencephalic cisterns. *B*, After *intravenous* contrast enhancement, tumor blush delineates the lesion more clearly (black arrow). *C*, After *intrathecal* contrast enhancement with metrizamide, the suprasellar component of the pituitary adenoma appears as a round filling defect in the opacified suprasellar cistern (white arrows). The perimesencephalic cistern which surrounds the midbrain (m) now appears white. Metrizamide also delineates the uppermost portion of the fourth ventricle and the cerebellar folia.

fied cerebrospinal fluid between a mass and the adjacent compressed brain identifies the mass as extra-axial rather then intrinsic. Metrizamide CT helps to distinguish an encephalocele from other midline basal masses by identifying a thin rim of density in the subarachnoid space surrounding the herniated brain.[40]

Communication Between Spaces

Conventional CT cannot always distinguish whether a ventricular system is patent or obstructed and cannot always distinguish whether an apparently uniform "cerebrospinal fluid space" within the brain represents a dilated ventricle or a large periventricular mass with the density of cerebrospinal fluid such as a porencephalic cyst which compresses the ventricle. Accurate diagnosis depends on a cerebrospinal fluid marker, such as metrizamide, placed into the lumbar thecal sac, or directly into the ventricle. Uniform opacification of the cerebrospinal spaces indicates patency of the system. Failure to opacify a portion of the "ventricle" or detection of an intervening linear lucency indicates non-communication and/or intervening membrane.[9,60]

Cerebrospinal Fluid Rhinorrhea

Leakage of cerebrospinal fluid poses the constant danger of meningitis and brain abscess. Successful surgical obliteration of the cerebrospinal fluid fistula requires accurate anatomic delineation of the bony and dural defects. Previous methods of demonstrating these fistulae were not always successful: Radionuclide cisternography usually documented the existence and general region of the fistula, but gave imprecise anatomic localization.[70] Cisternography with pantopaque sometimes failed to fill the fistula because of the high viscosity of pantopaque, and always left an oily residuum in the intracranial space. Metrizamide CT cisternography now appears to be very helpful in documenting the site of leakage[10] (Fig. 15). After metrizamide is instilled into the subarachnoid space, the patient is placed into that position which causes maximal leakage of cerebrospinal fluid, and CT scans of the basal cisterns, base of the skull, and paranasal sinuses are obtained. CT identification of a contrast-air level in a specific sinus documents the site of exit. If exit is via the sella turcica into the sphenoid sinus ("empty sella"), CT also demonstrates intrasellar contrast agent. Re-scanning in a second position demonstrates shift of contrast fluid levels within the sinus and helps to confirm that the sinus filled by contrast is the primary site of leakage, not merely the most dependent sinus collecting drainage from another primary site. Cotton pledgets may be used to occlude the various orifices before scanning as is done in radionuclide studies. Increased density of *one* pledget shows the site of leakage.

Cerebrospinal Fluid Dynamics — Communicating Hydrocephalus

Metrizamide CT cisternography provides a new method for evaluating patients with dementia for possible communicating hydrocephalus. This technique combines the anatomic detail of high quality pneu-

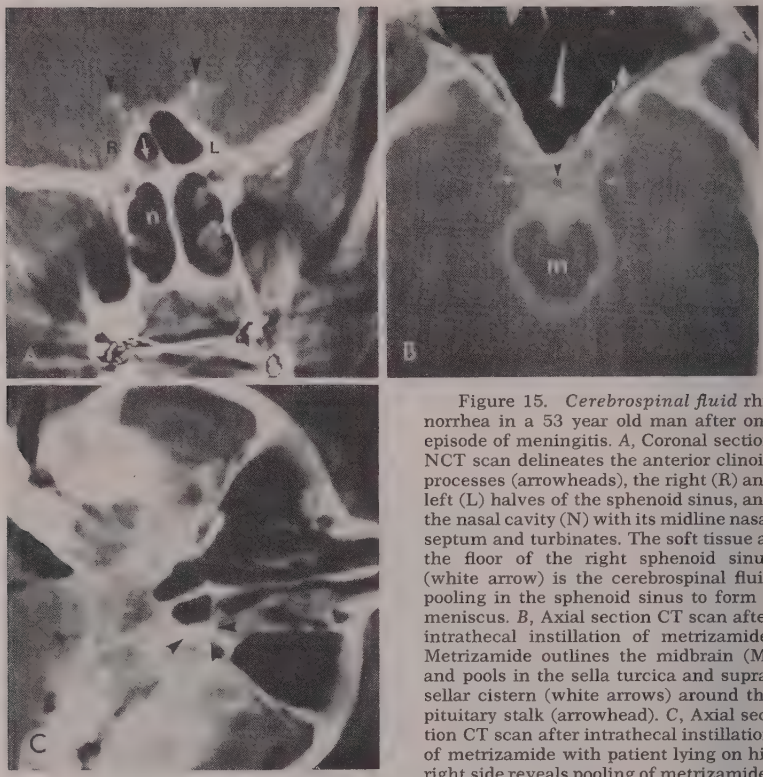

Figure 15. *Cerebrospinal fluid* rhinorrhea in a 53 year old man after one episode of meningitis. *A*, Coronal section NCT scan delineates the anterior clinoid processes (arrowheads), the right (R) and left (L) halves of the sphenoid sinus, and the nasal cavity (N) with its midline nasal septum and turbinates. The soft tissue at the floor of the right sphenoid sinus (white arrow) is the cerebrospinal fluid pooling in the sphenoid sinus to form a meniscus. *B*, Axial section CT scan after intrathecal instillation of metrizamide. Metrizamide outlines the midbrain (M) and pools in the sella turcica and suprasellar cistern (white arrows) around the pituitary stalk (arrowhead). *C*, Axial section CT scan after intrathecal instillation of metrizamide with patient lying on his right side reveals pooling of metrizamide-opacified CSF in the dependent portion of the right sphenoid sinus (arrowheads). This indicates that the leakage occurs through the roof of the right sphenoid sinus. After surgical exposure of the right sphenoid sinus from below, tiny droplets of clear fluid could be seen forming at several sites along the roof of the right sphenoid sinus. Packing this sinus with muscle and fat terminated the cerebrospinal fluid leak.

mography with physiologic data comparable to radionuclide cisternography.[8, 9, 73, 74] It also provides two new differential criteria: evidence of periventricular edema, and degree of brain absorption of contrast agent. Metrizamide CT studies should eliminate most of the 10 to 20 per cent of test failures documented to occur with radionuclide studies.[30] Otherwise metrizamide CT cisternography is similar to the radionuclide cisternogram. Investigators have performed both studies simultaneously by injecting the metrizamide and the radionuclide together.

Drayer, Rosenbaum, and Higman have established preliminary criteria for normal and abnormal cerebrospinal fluid dynamics by metrizamide CT cisternography, as performed by their method with serial CT scans obtained immediately after injection and at 6 hour intervals for as long as necessary. In the normal patient, metrizamide opacifies the

basal subarachnoid cisterns, pericerebellar cisterns, and Sylvian fissures symmetrically at 0 hours, and opacifies the cortical sulci and interhemispheric fissures at 6 hours. The fourth ventricle opacifies by reflux routinely at 0 hours. The lateral and third ventricles may be opacified by reflux immediately, and, *if so*, show continued (but decreasing) opacification on the 6 and even 12 hour scans as well. There is a distinct blush of the cerebral and cerebellar substance adjacent to the opacified cisterns at 12 and 24 hours. This fades by 36 to 48 hours (Fig. 16).

In patients with communicating hydrocephalus, a different, "delayed" pattern of metrizamide flow is observed. There is greater entry of metrizamide into the ventricular system resulting in higher density measurements by CT, and stasis of the contrast agent within the ventricle at 24 and even 48 hours (Fig. 17). Occasionally metrizamide enters the ventricles late, not initially, suggesting reversal of normal cerebrospinal fluid net flow. These patients may exhibit asymmetric filling of the Sylvian fissures, a diminished cerebral blush in the parasagittal region, and a thin lucent band circumscribing the intraventicular contast agent. This band appears to represent periventricular edema (Fig. 17). Utilization of the digital data from the serial CT scans provides an approach to estimating the kinetics of cerebrospinal fluid production and wash-out of metrizamide from the ventricle.[8, 9, 60, 61, 69]

Drayer et al. also observed an intermediate pattern of metrizamide flow,[8] which consists in ventricular stasis of metrizamide at *lower concentration* than seen with communicating hydrocephalus; a normal parasagittal cerebral blush; and no perventricular edema. Patients with this pattern probably have partial cerebrospinal fluid subarachnoid absorption defects and carry diagnoses of Alzheimer's disease and resolving or progressive stages of meningitis and subarachnoid hemorrhage.[8]

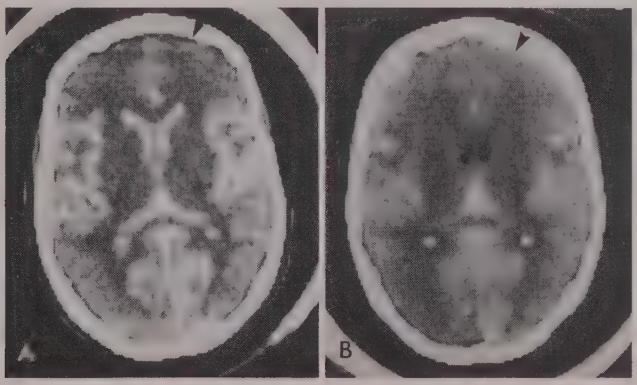

Figure 16. Metrizamide CT Cisternography. Normal Dynamics. *A*, CT at zero hours, after intrathecal instillation of metrizamide. Ventricular reflux fills the lateral ventricles, Sylvian fissure and adjacent sulci symmetrically. The ventricles are not enlarged. There is no periventricular edema or parenchymal brain blush. *B*, CT 8 hours later reveals marked clearing of metrizamide from the ventricles and beginning parenchymal brain blush (arrowhead). (Compare the density of the frontal and occipital lobes with that in *A*. Images exposed at identical settings).

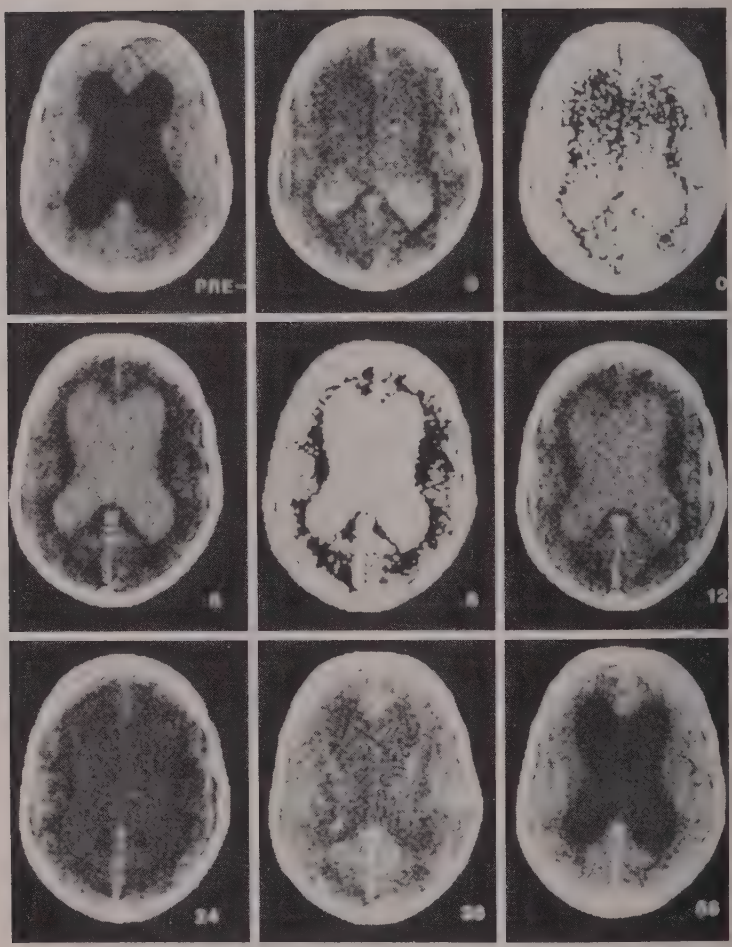

Figure 17. Metrizamide CT Cisternography. Abnormal Cerebrospinal Fluid Dynamics. PRE, Preliminary NCT reveals large, bilaterally symmetric lateral ventricles, but normal cortical sulci. The ventricular margin is slightly irregular.

Serial axial CT scans at the same level after intrathecal administration of metrizamide reveal progressive changes: At 0 hours, metrizamide opacifies the lateral ventricles, but layers posteriorly since the patient is in brow-up position. A thin lucent perimeter between the opacified ventricles and the surrounding brain represents periventricular edema which may be related to transependymal resorption of cerebrospinal fluid. At 6 hours the metrizamide has diffused evenly throughout the lateral ventricles. At 12 hours, a high concentration of metrizamide persists within the lateral ventricles. No parasagittal blush could be discerned on vertex cuts (not shown). With continued reduction in metrizamide concentration, the ventricles become isodense with brain at 24 hours, less dense than brain at 36 hours, and nearly their original cerebrospinal fluid density at 56 hours. (*From* Drayer, B. P., Rosenbaum, A. F., and Higman, H. B.: Neuroradiology, *13*:7–17, 1977. By permission.)

CT OF THE SPINAL COLUMN, CORD, AND OTHER STRUCTURES

Spinal Cord

Computed tomography may be utilized to delineate the cervical spinal cord and cervical subarachnoid space. The normal cervical cord appears as a homogeneous central density surrounded by a low density halo of cerebrospinal fluid. The epidural space and spinal canal appear as concentric rings of increased density external to the cerebrospinal fluid (Fig. 18*A*). Osteophytes, disk protrusions, fracture fragments and tumors which encroach on the spinal canal may be delineated as masses of abnormal density which narrow the bony canal, compress the sub-

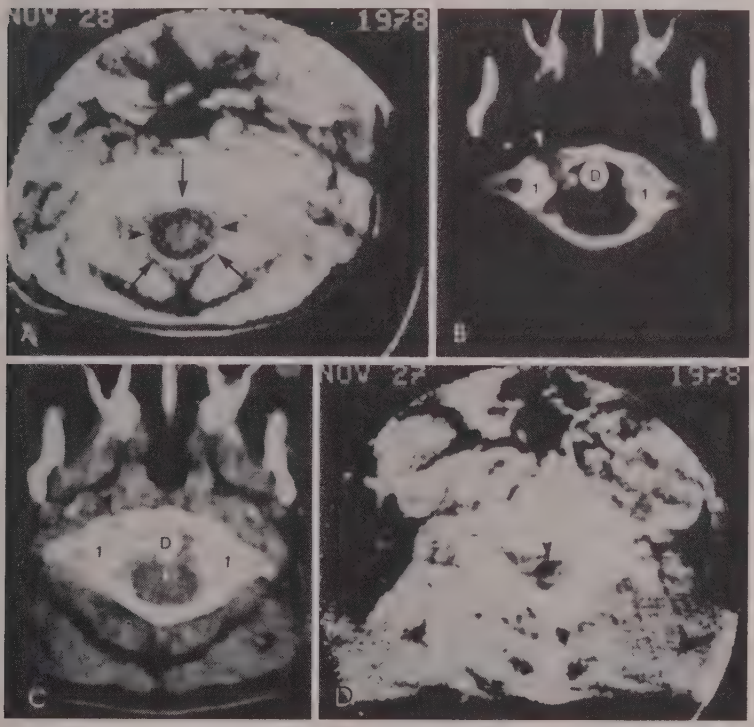

Figure 18. *CT of the Spinal Cord. A*, Normal spinal cord at the level of the C2 body. NCT clearly delineates the lucent halo of the subarachnoid space (arrowheads) and the central nearly homogeneous density of the spinal cord. The cervical epidural space (arrows) has a density which is intermediate between the bone and the lucent subarachnoid space. *B* and *C*, Fracture of C1 with compression of the subarachnoid space. *B*, NCT at the level of the C1 ring (1, 1) and dens (D). When adjusted to show bone detail, this NCT reveals a comminuted fracture of the lateral mass of C1 (white arrowhead). *C*, The identical NCT, adjusted to show soft tissue detail. The fragments and associated soft tissue are displaced posteriorly and narrow the ventral subarachnoid space (white arrowhead), but do not compress the spinal cord itself. *D*, *Syrinx*. NCT at the level of C4 reveals a very lucent defect (arrowhead) in the central portion of the spinal cord which corresponds to the patient's known syrinx.

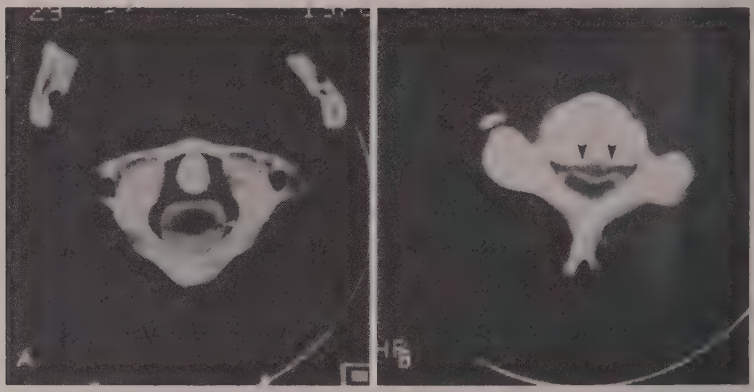

Figure 19. *Metrizamide CT of the Spinal Canal. A, Normal.* At the level of the C1 ring and dens, NCT reveals the whole halo of the metrizamide-opacified subarachnoid space, the central spinal cord and the posterior nerve roots bilaterally (little white arrow). The cervical epidural space appears lucent with respect to the metrizamide-opacified cerebrospinal fluid, but is denser than nonopacified cerebrospinal fluid (see Figure 18*A*). *B, Cervical disk.* At the level of the C3–C4 intervertebral disk space, CT reveals marked posterior displacement of the metrizamide-opacified cerebrospinal fluid and the cervical spinal cord by a large, partially calcified cervical disk (arrowheads).

arachnoid space, and/or compress the spinal cord. Intrinsic lesions of the cord such as astrocytoma and syrinx may also be demonstrated (Fig. 18*C*). The thoracic spinal cord and cauda equina are visualized less well than the cervical cord.

If intravenous contrast agent is administered, contrast agent within the epidural space increases the density of the epidural space and the difference in density between the blushing epidural space and nonblushing cerebrospinal fluid. Use of intravenous contrast agent therefore affords improved delineation of the subarachnoid space and compression of that space by pathology. Use of intravenous contrast agent also delineates the vertebral arteries and epidural veins within the spinal canal.

If metrizamide is instilled into the lumbar cerebrospinal fluid prior to CT scanning, the entire spinal cord and subarachnoid space may be outlined in detail at any level.[6, 53] (Fig. 19*A*). Even the dorsal and ventral nerve roots emerging from the cord may be demonstrated. Compression of the subarachnoid space and spinal cord by herniated disks, ridges and neoplasms is clearly defined (Fig. 19*B*).

Spinal Column

Computed tomography delineates the anatomy of the spine in great detail. The vertebral bodies, pedicles, transverse processes, laminae, spinous processes and articular pillars are shown almost as well as on dried anatomic specimens (Fig. 20). Because the CT section is oriented perpendicular to the spine, CT demonstrates a cross section of the spinal canal, and delineates clearly whether tumors, osteophytes or fracture fragments narrow the spinal canal and/or neural foramina (Fig. 20). In

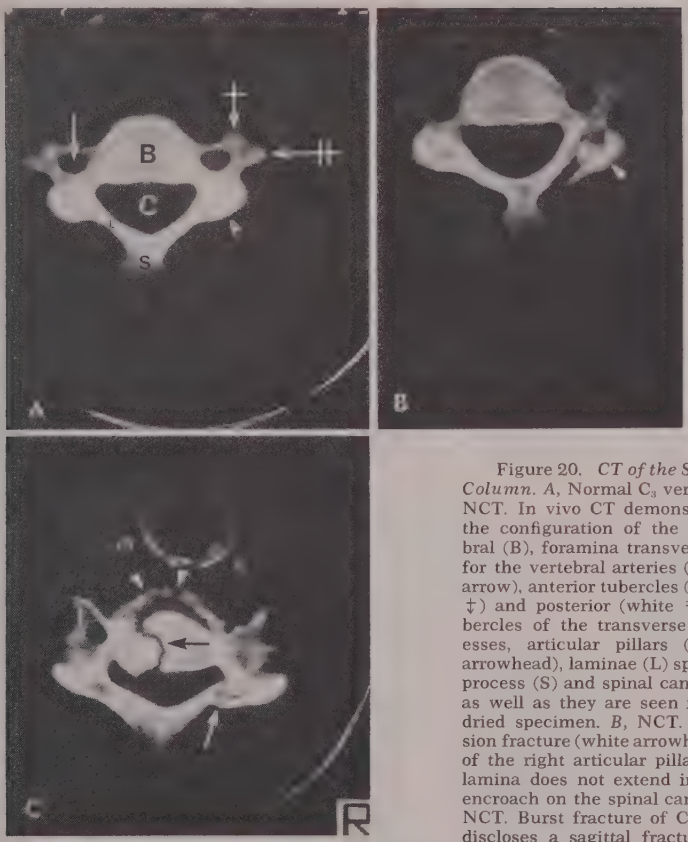

Figure 20. *CT of the Spinal Column. A,* Normal C_3 vertebra. NCT. In vivo CT demonstrates the configuration of the vertebral (B), foramina transversaria for the vertebral arteries (white arrow), anterior tubercles (white ‡) and posterior (white ∓) tubercles of the transverse processes, articular pillars (white arrowhead), laminae (L) spinous process (S) and spinal canal (C) as well as they are seen in the dried specimen. *B,* NCT. Avulsion fracture (white arrowheads) of the right articular pillar and lamina does not extend into or encroach on the spinal canal. *C,* NCT. Burst fracture of C6. CT discloses a sagittal fracture of the vertebral body (←), comminuted avulsion fracture of the anterior cortical margin (white arrowheads), fracture of the right lamina (white arrow) and marked compression of the spinal canal (compare with *A*).

our opinion, the images obtained by computed tomography are clearly superior to those obtained by conventional transaxial tomography.[29]

Patients with acute spinal trauma may have their fractures identified by plain radiographs, stabilized by tong traction, as necessary, and then studied in detail by CT to determine the advisability of surgical intervention.[6, 53] Coupled with CT delineation of the spinal cord (and perhaps with use of metrizamide), sufficient information may be obtained to guide management of these patients (Figs. 18 and 20).

Calvarium

Routine CT images are inadequate for evaluating bone. Adequate demonstration of bony detail requires use of wide window widths and high window levels, typically a 400 unit window width and a 100 to 500

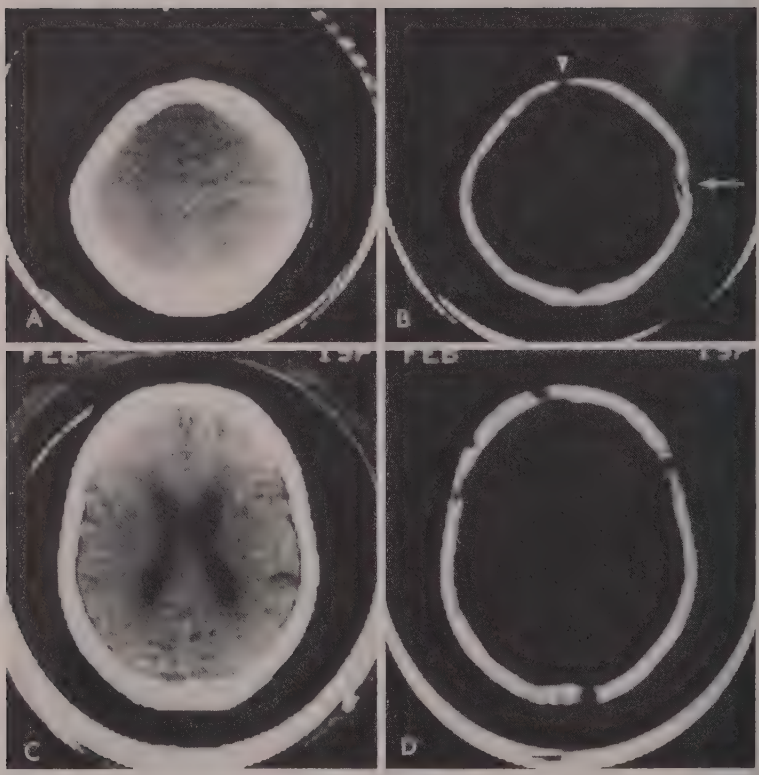

Figure 21. Calvarium (Bone Detail). *A* and *B*, Depressed skull fracture in a 3 year old boy. *A*, Routine NCT (window width 100, window level 25) exposed for *intracranial* detail appears normal. *B*, The *identical* section (window width 400, window level 369) exposed for bony detail reveals a right parietal skull fracture with 6 mm depression (white arrow) and the sagittal suture (white arrowhead). *C* and *D*, Metastatic breast carcinoma in a 69 year old woman. *C*, Routine NCT shows no abnormality. *D*, Bone detail exposure of the *identical* section demonstrates bilateral multifocal calvarial metastases.

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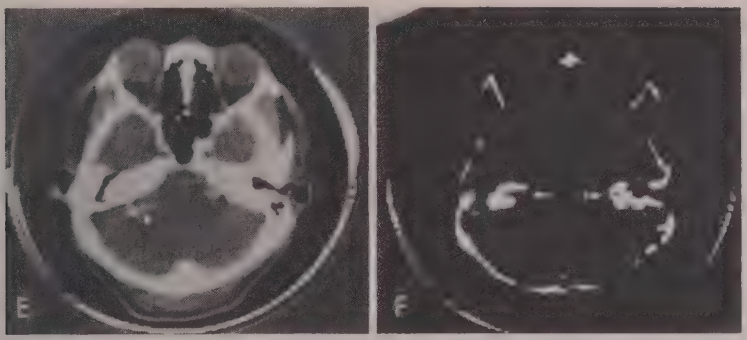

Figure 21 *Continued.* *E* and *F*, Left acoustic neuroma in a 37 year old man. *E*, Routine NCT reveals only residual pantopaque (white arrowhead) in the left cerebellopontine angle. *F*, Bone-detail exposure of the identical section reveals marked, asymmetrical flaring of the left internal auditory canal (white arrow) as compared to the right (crossed white arrow).

unit window level on EMI equipment.[33, 36] Lesions of the scalp, fractures, metastases to the calvarium, hyperostosis, and erosion of the sella turcica and porus acusticus may not be appreciated at all unless specifically sought on such "bone-detail" CT images (Fig. 21). CT scans from each patient with trauma, with possible metastases, with a juxta-osseous lesion that could be a meningioma, or with a basal mass near to the sella turcica or cerebellopontine angle should be viewed on the television display at "bone-detail" settings to avoid misdiagnosis.

Tumors of the Paranasal Sinuses

CT adds a new dimension to understanding and staging sinus tumors by demonstrating both the soft tissue and the associated bone destruction.[25] Serial axial and coronal CT sections through the sinuses, orbits, skull base and pharynx define accurately the site, size and extension of sinus lesions and aid in planning surgical and nonsurgical management of these masses (Fig. 22).

Neuromuscular Disease

CT may be utilized to help determine the extent and distribution of denervation atrophy and primary muscle degeneration[52, 58] (Fig 23). Normal muscle appears nearly homogeneous in density. The fibrous intermuscular septa and blood vessels are outlined by relatively small amounts of surrounding fat. With loss of muscle, patchy and diffuse zones of lucency replace the normally dense muscle bundles and the muscle bulk decreases. The blood vessels and fibrous intermuscular septa become relatively more prominent. With severe muscle loss, only the ghosts of muscle bundles, the blood vessels and the septa may be detected in a field of uniform lucency which is presumed to represent fatty replacement of the muscle.

With experience and knowledge of the normal sectional anatomy of the extremities, it is possible to name the muscles most affected for correlation with the clinical picture and biopsy data. It is hoped that CT

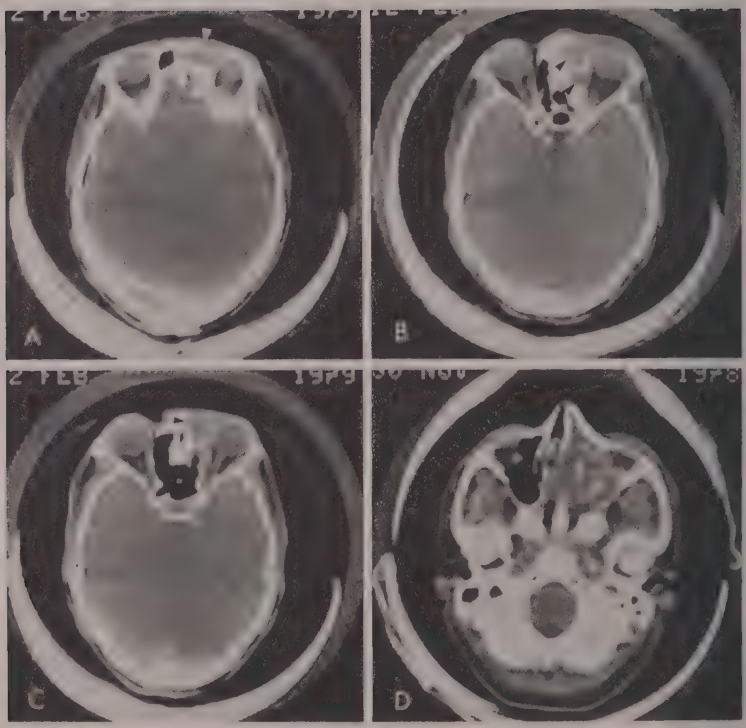

Figure 22. *Sinus Lesions. A, B, C,* Benign, right fronto-ethmoidal mucocele, NCT scan. A homogeneous soft tissue mass fills and expands the right frontal sinus (arrowhead in A) and the right ethmoidal sinuses (arrowheads in B) and erodes into the right orbit to displace the globe anteriorly and to the right. *D, E, F,* Malignant adenocarcinoma of the paranasal sinuses. *D,* Axial section NCT reveals soft tissue mass filling the nasal cavity and right maxillary sinus, destroying the intervening bony walls.

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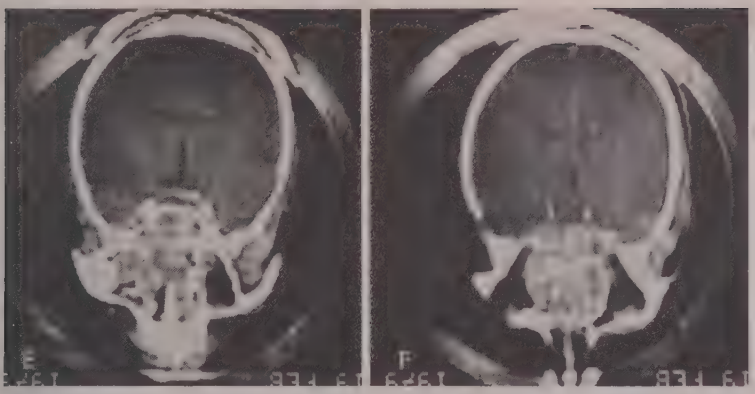

Figure 22 *Continued.* *E*, Coronal section NCT (with right to the reader's left) shows the tumor extension through the nasal cavity, right maxillary antrum, a portion of the left maxillary antrum and the sphenoid sinus. *F*, Coronal section NCT at the level of the planum sphenoidale shows tumor growth into the anterior cranial fossa with invasion of the gyri recti bilaterally (white arrows).

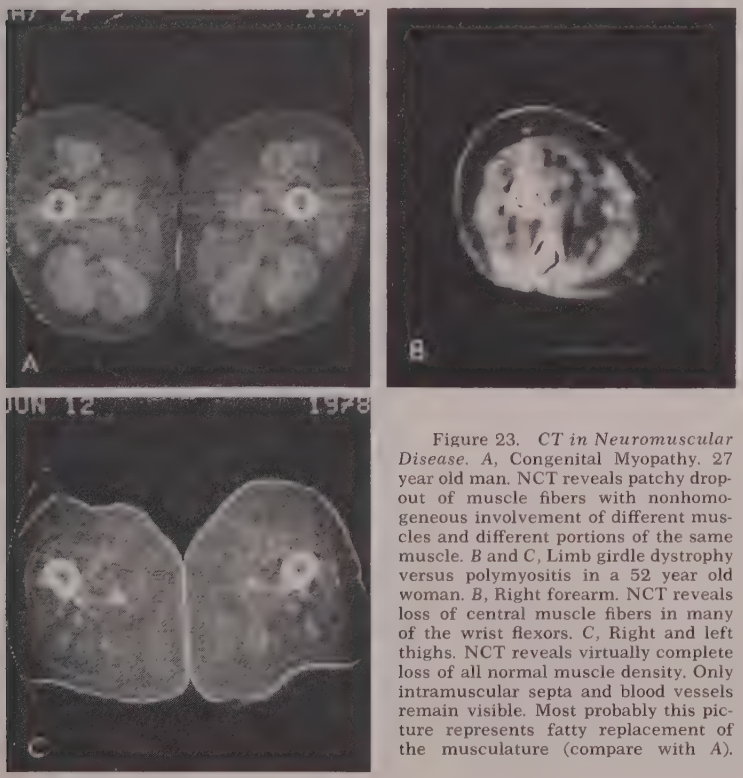

Figure 23. *CT in Neuromuscular Disease.* *A*, Congenital Myopathy. 27 year old man. NCT reveals patchy dropout of muscle fibers with nonhomogeneous involvement of different muscles and different portions of the same muscle. *B* and *C*, Limb girdle dystrophy versus polymyositis in a 52 year old woman. *B*, Right forearm. NCT reveals loss of central muscle fibers in many of the wrist flexors. *C*, Right and left thighs. NCT reveals virtually complete loss of all normal muscle density. Only intramuscular septa and blood vessels remain visible. Most probably this picture represents fatty replacement of the musculature (compare with *A*).

delineation of muscle wasting may help to characterize neuromuscular disease and help to guide biopsy.

CT-GUIDED BIOPSY

In patients with lesions which are inaccessible surgically and in patients with complex clinical courses in whom a given lesion may represent primary neoplasm, metastasis, hemorrhage, infarction, or supervening infection, CT now provides a method for guiding a biopsy needle into the lesion to achieve accurate diagnosis with little morbidity[42, 48] (Figs. 9, 24, 25). CT-guided tumor biopsy provides tissue for accurate histologic diagnosis. Inhomogeneous tumors may be sampled at multiple, predetermined sites to assess overall malignancy, permitting rational choice of radiotherapeutic and/or chemotherapeutic protocol. CT scans obtained with the needle in situ document the exact site of each biopsy, so there is no question whether the region sampled lay within the main lesion or merely at its edge when the histology report returns "gliosis" or "nonspecific inflammation." Similarly when aspiration of a supposedly cystic lesion returns no fluid, CT documents the "intracystic" location of the needle tip, obviating repeated blind probing of the brain in an attempt to aspirate the occult cyst.

Aspiration of cystic tumors effects immediate decompression and palliation with significant symptomatic relief at low morbidity (Fig. 24). This technique may be symptomatically beneficial for terminal patients with recurrent lesions of known histology. Aspiration of abscesses documents the diagnosis. Each locule of a multiloculated collection may be drained separately (Fig. 25). Control CT scans during the procedure ensure that no daughter lesions are left untreated. Aspiration also provides material for both immediate Gram stain to select interim antibiotic coverage and for culture and sensitivity studies to select definitive antibiotic treatment. Antibiotic irrigation of the abscess cavity via the biopsy needle may contribute to therapy.

In our series of aspiration biopsies, most lesions were entered on the first pass. No patient suffered worsening of neurological status. A few suffered small, clinically insignificant CT documented hemorrhages into the lesions after biopsy.

PHYSIOLOGIC STUDIES WITH COMPUTED TOMOGRAPHY

Positron Emission Transaxial Tomography (PETT)

A number of radioactive elements including ^{15}O, ^{13}N, ^{11}C and ^{18}F emit positrons as they decay. These positrons travel distances of 1 to 6 mm and then combine with an electron. The electron and positron annihilate each other, convert their mass to energy and emerge as two annihilation photons of 511 kev (kiloelectron volts) each. These annihilation photons always travel in 180 degree opposing directions. Thus, their path constitutes a straight line. If two (or more) scintillation detectors are aligned to

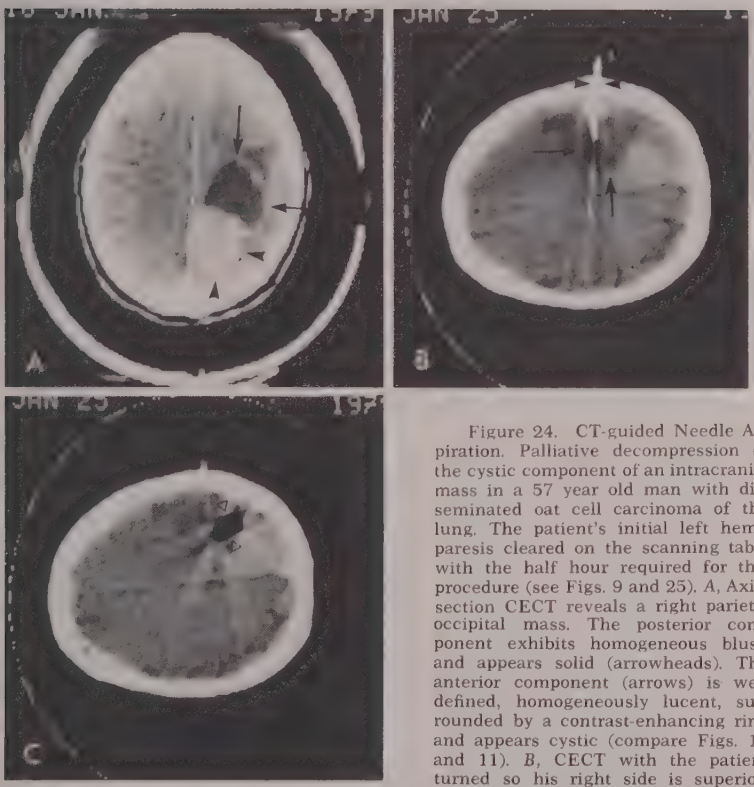

Figure 24. CT-guided Needle Aspiration. Palliative decompression of the cystic component of an intracranial mass in a 57 year old man with disseminated oat cell carcinoma of the lung. The patient's initial left hemiparesis cleared on the scanning table with the half hour required for this procedure (see Figs. 9 and 25). *A*, Axial section CECT reveals a right parieto-occipital mass. The posterior component exhibits homogeneous blush and appears solid (arrowheads). The anterior component (arrows) is well defined, homogeneously lucent, surrounded by a contrast-enhancing rim, and appears cystic (compare Figs. 10 and 11). *B*, CECT with the patient turned so his right side is superior, demonstrates placement of an aspiration needle (arrowheads) into the lucent component (arrows) of the lesion. CT documents the exact position of the needle tip with respect to the various components of the mass. *C*, Suction aspiration drained 30 cc of clear yellow fluid. Air (open arrowheads) now outlines the reduced size of the cavity after aspiration. There is no evidence of hemorrhage.

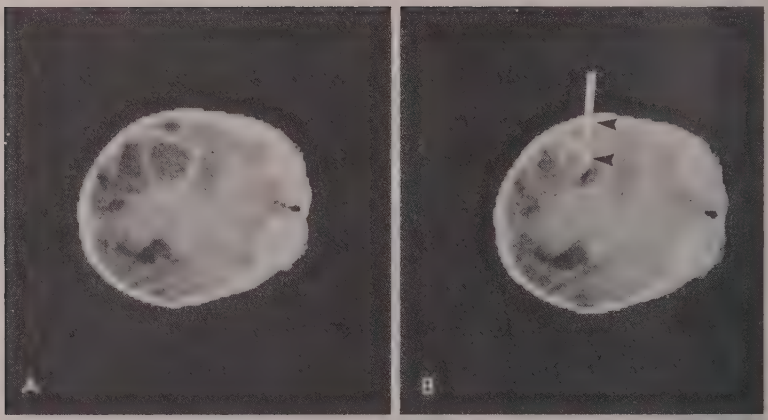

Figure 25. CT-guided aspiration of multilocular abscesses in a 4 year old boy. CECT scans. *A*, Prior to aspiration, CECT reveals three loculated abscesses, surrounding edema and obliteration of the left lateral ventricle. *B*. Intra-procedural CECT shows the aspiration needle (arrowheads) positioned within the deepest of the collections. The course of the needle outside the abscess reproduced poorly and is therefore indicated by a white line.

face each other across the field of radioactivity, and if the detectors are gated electronically to record only those scintillations that occur at the same time (in coincidence), then the detectors will record only those photons that arise simultaneously and travel in a straight line to hit the two detectors simultaneously. The detectors, therefore, record only the annihilation photons that arise in the narrow cylindrical volume stretching between the two opposed detectors.

With multiple pairs of detectors, proper collimation, sophisticated electronics, rotation of the detectors with respect to the patient (or vice versa) and computer reconstruction algorithms such as are used in conventional computed tomography, it is possible to obtain multilevel digital and analog pictures of the distribution of the annihilation radiation in patients. Thus, if positron emitting radiopharmaceuticals such as $^{11}CO_2$, $C^{15}O_2$, $H_2{}^{15}O$, $^{13}NH_3$, etc., are administered to a patient, it is possible to determine the distribution of these radiopharmaceuticals *in vivo* to within the 1 to 6 mm travel distance of the photons by mapping the distribution to the annihilation reactions. This process is called positron emission transaxial tomography (PETT) [66, 75] (Fig. 26).

The energy of the annihilation radiation (511 kev) is higher than that of the commonly used radionuclides such as technetium (140 kev), so the photons penetrate tissue more easily. The annihilation radiation arising deep within the brain is able to reach and energize the detectors; "deep" events are not lost to the study as is the case in conventional radionuclide studies. Because the positron-emitting radionuclides of interest have extremely short half-lives (^{15}O 2.05 min; ^{13}N 9.96 min; ^{11}C 20.34 min; ^{18}F 110 min), large radiation doses may be administered to the patient safely to improve imaging and accuracy. Determination of many different metabolic compartments can be performed in rapid sequence without degradation of information by residual background activity.

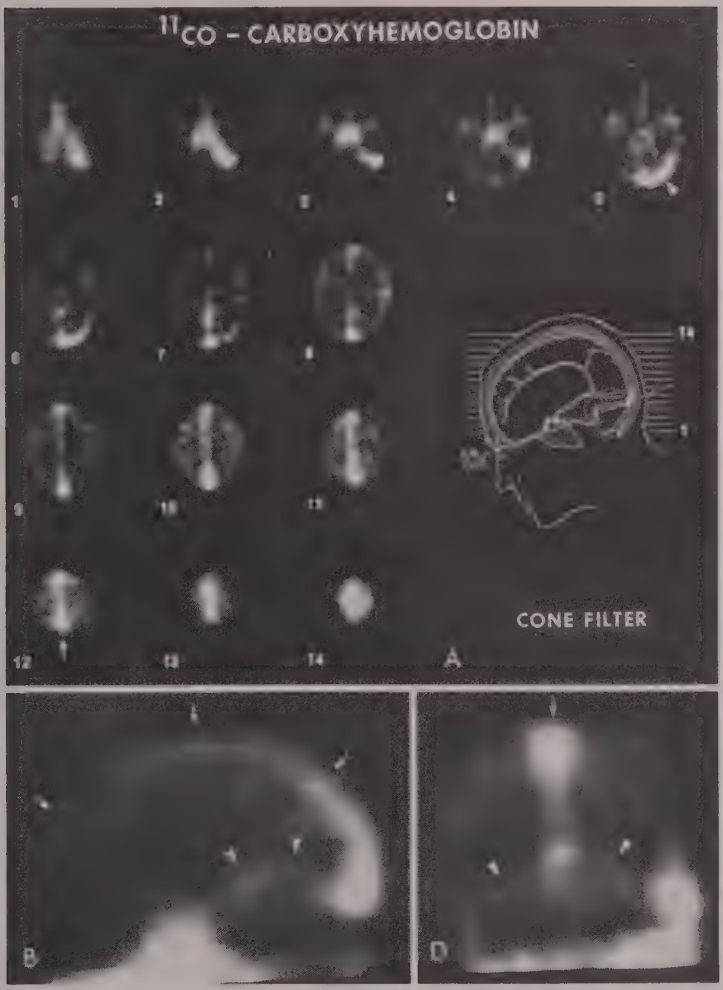

Figure 26. *Positron-Emission Transaxial Tomography (PETT).* Cerebral Blood Volume. *A*, Serial axial images, oriented as shown in the accompanying diagram. PETT with ^{11}CO-carboxyhemoglobin images the blood pool and delineates the major venous sinuses such as the transverse sinus (white arrowhead in image 5) and the superior sagittal sinus (white arrow in image 12). The parasellar, Sylvian and interhemispheric vessels are shown as composite densities in images 2 to 5. The gray matter and white matter are distinguished by virtue of their different vascularity. *B*, Sagittal reconstruction of the serial axial images (anterior to the reader's left) delineates the superior sagittal sinus (white arrows) and transverse sinus (white arrowheads). *C*, Coronal reconstruction of the serial axial images again demonstrates these structures.

Ter-Pogossan, Raichle and other investigators[4, 66, 75] have now demonstrated that PETT can determine, in vivo, the regional cerebral blood volume, quantitative measurements of regional metabolism, regional fractional oxygen extraction and regional tissue chemical composition.

For example, inhalation of trace amounts of ^{11}C-labelled carbon monoxide achieves in vivo labelling of hemoglobin (^{11}C - carboxy hemoglobin). Images of the distribution of the ^{11}C - carboxy hemoglobin delineate the blood pool and, thereby, depict the major venous sinuses, the gray matter, and the white matter by virtue of their differing blood density (Fig. 26).[4, 66]

Quantitative data from PETT, obtained at equilibrium as counts sec^{-1} tissue ml ^{1} and a simultaneous peripheral venous blood sample as counts sec^{-1} (gm blood)$^{-1}$ permit calculation of regional cerebral blood volume by

$$\frac{(\text{counts})\,(\text{sec}^{-1})\,(\text{ml tissue})^{-1} \times 100}{(\text{counts})\,(\text{sec}^{-1})\,(\text{gm blood})^{-1}\,\rho\,\delta f}$$

where ρ is the density of blood (approximately 1.05 gm ml), δ is the tissue density (approximately 1.05 gm/ml) and f is the ratio of mean tissue hematocrit (approximately (0.85). Measurements of regional blood volume provide a key element in the equations for calculating other biologic parameters. For example, measurements of regional blood volume and sequential quantitative determinations of the regional equilibrium distribution of ^{11}C-labelled methyl albumin provide data for calculating the regional tissue hematocrit.

PETT studies utilizing ^{11}C-labelled glucose or the substrate analog ^{18}F-2-deoxy D-glucose permit determination of regional cerebral glucose metabolism[66] (Fig. 27). Studies using positron-emitting radiopharmaceuticals which distribute rapidly to both blood and tissue permit quantitative determination of the regional tissue-blood partition coefficient and the regional tissue concentration of the labelled substance. Thus with ^{11}C-carbon dioxide one can quantitate the brain tissue acid-base balance in vivo.[66] Sequential PETTS after inhalation of trace amounts of ^{15}O-labelled oxygen and ^{15}O-labelled carbon dioxide to equilibrium provide a means of calculating the regional fractional oxygen extraction. Measurements of regional cerebral blood flow have not yet been achieved by PETT, but appear within reach.

Xenon Enhancement Tomography (XET)

Xenon is a *fat soluble*, chemically inert, nonradioactive gas with a high atomic number (54) which enables it to act as a contrast agent for CT studies. Xenon readily crosses the blood-brain barrier, diffuses freely in brain tissue, and enhances the *normal* brain. Conventional intravenous iodinated contrast agents cross the blood-brain barrier only where it is abnormally leaky and enhance regions of abnormality. Thus, stable xenon provides information which is very different from that obtained from conventional studies. Unfortunately, xenon is expensive. Its use requires intubating patients since xenon induces sleep or anesthesia at the concentrations *presently* necessary to achieve adequate contrast enhancement.

The distribution of xenon depends on the regional lipid content, regional perfusion, and regional tissue-blood partition coefficient. Since the lipid content of normal white matter (14 to 23 per cent) exceeds that of normal gray matter (4 to 8 per cent), the equilibrium concentration of xenon in white matter exceeds that in gray matter (Fig. 28). Static xenon images obtained by conventional CT after a patient has breathed 70 per cent xenon to equilibrium show increased density of the white matter relative to the gray matter (xenon enhancement). Lesions which lower the lipid content focally may appear as focal zones of decreased or absent xenon enhancement. Multifocal plaques of multiple sclerosis have been detected by xenon-enhanced CT when they were not detectable by routine and iodine-enhanced CT scans.[64] Similarly, isodense subdural hematomas which appear invisible on conventional CT scans, have been detected as non-(xenon) enhancing masses which displace the xenon-opacified brain.[80] Tumors and mature cerebral infarctions exhibit low xenon uptake and appear as filling defects in the otherwise enhancing brain.[65] Recent cerebral infarctions show delayed xenon uptake at the periphery and sometimes throughout the lesion. Such diminished uptake appears to reflect diminished perfusion of potentially viable tissue and

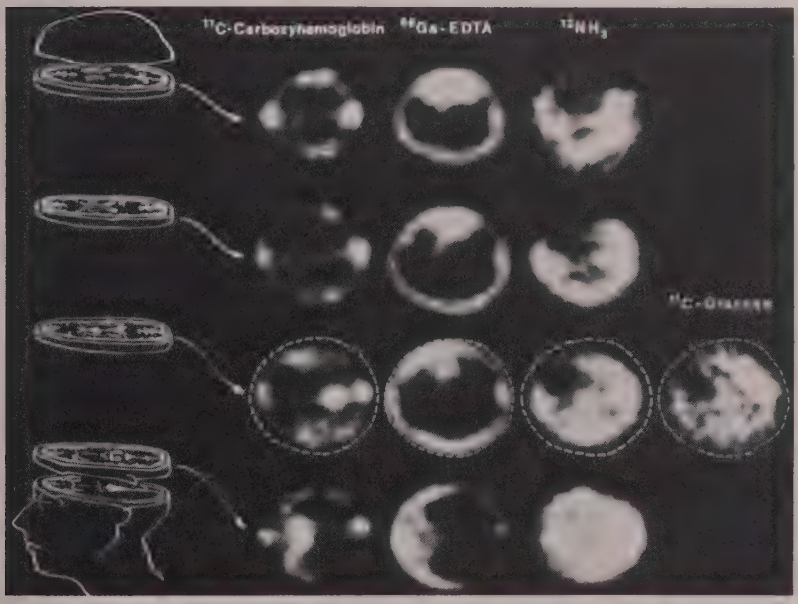

Figure 27. Right cerebral infarction. PETTs with serial isotopes at 4 different brain levels. PETT with ^{11}C-carboxy hemoglobin demonstrates a diminished blood volume in the region of infarction. PETT with ^{68}Ga-EDTA demonstrates marked uptake representing damage to the blood-brain barrier in the same region. PETT with $^{13}NH_3$ demonstrates an even larger right cerebral defect which probably represents both diminished perfusion in the infarction and disruption of metabolic pathways, with failure to retain $^{13}NH_3$ in the peri-infarction zone. PETT with ^{11}C-glucose demonstrates a focal defect in glucose metabolism in the region of infarction.

may prove to be a valid prognostic sign.[65] The relative degree of diminished uptake on XET does not appear to help differentiate between infarction and tumor or to differentiate among the various types of tumor.[65]

If the patient is permitted to breathe xenon to an equilibrium concentration and if the xenon is withdrawn abruptly after equilibrium has been established, then the regional wash-out of xenon will reflect the regional blood flow and regional tissue-blood partition coefficient[32] (Fig. 28). Rapid, sequential CT scans obtained during xenon washout, would then provide data helpful in quantitating regional blood flow and regional partition coefficients. Utilizing xenon washout studies in baboons, Drayer et al. have demonstrated direct correlation between end-tidal xenon concentration, arterial xenon concentration, and the degree of CT enhancement.[11] They have also demonstrated a mild increase in regional blood flow in normal brain when the partial pressure of CO_2 ($PaCO_2$) was increased to 60 to 65 torr, and a prominent decrease in regional blood flow in normal brain when the $PaCO_2$ was decreased to 15 to 20 torr.[11]

As scanner technology permits rapid sequence simultaneous multilevel scans, these techniques may permit practical clinical demonstration of regional blood flow.

FUTURE ADVANCES

The normal arteriovenous circulation time through the brain is approximately 2.5 to 6.0 seconds. As CT scanners achieve scan times of 1 second or less, *computed angiography* becomes possible. This is expected to permit CT delineation of the arterial supply and venous drainage of a lesion, and of regions of subtly diminished perfusion.

Still in development, *nuclear magnetic resonance (NMR)* is another tool capable of imaging thin cross-sections of the body.[26, 27, 28] Like CT, NMR data may be digitized and processed to display gross anatomy, characterize the tissue components present and provide an approach to obtaining physiologic data. Unlike CT, NMR employs magnetic fields and non-ionizing radiofrequency energies considered harmless.[26–28] The plane of the NMR image is controlled by the orientation of the magnetic fields, not by a fixed scanning gantry, so that immobilized patients may be scanned in any desired plane.

NMR technology is highly complex. It depends on detection of the interaction between the magnetic fields of individual nuclei and the carefully contrived, deliberately varying magnetic fields induced around them. The signal observed varies with the strength of the magnetic field, the individual nuclei studied, the concentration of those nuclei in an area, and the molecular environment of these nuclei (i.e., the chemical compounds in which they are located and the liquidity or solidity of the structure). The nuclei ^{1}H, ^{13}C, ^{14}N, ^{17}O, ^{23}Na, ^{31}P and ^{43}Ca found in vivo, can be utilized for NMR imaging. Of these, the proton ^{1}H gives the strongest NMR signal. The distribution of other nuclei (notably ^{19}F) may also be imaged by NMR, permitting introduction of tracer elements (contrast agents) for evaluating a variety of metabolic parameters.

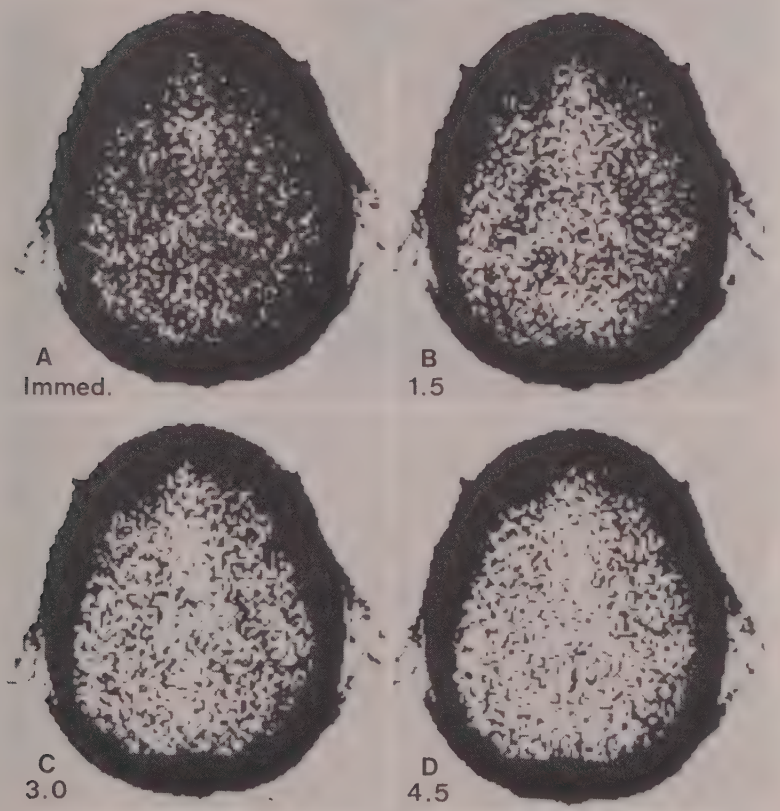

Figure 28. Xenon-Enhanced CT. Normal Saturation with Xenon and Normal Xenon Clearance. The images are displayed as black for white reversals at measure mode, so the calvarium appears as a black rim and each black dot represents a volume of brain with an EMI number of 27 units or greater. Case courtesy of Burton P. Drayer, University of Pittsburgh Health Center. *A*, CT immediately after discontinuation of xenon inhalation (70 per cent saturation) reveals the normal pattern of xenon uptake (black dots) and the central, non-enhancing lateral ventricles. *B* through *D*, Serial CT images at the same level at 1.5, 3.0 and 4.5 minutes after abrupt discontinuation of xenon inhalation demonstrates the pattern of xenon wash-out from normal brain. These serial images provide data for evaluating the kinetics of wash-out.

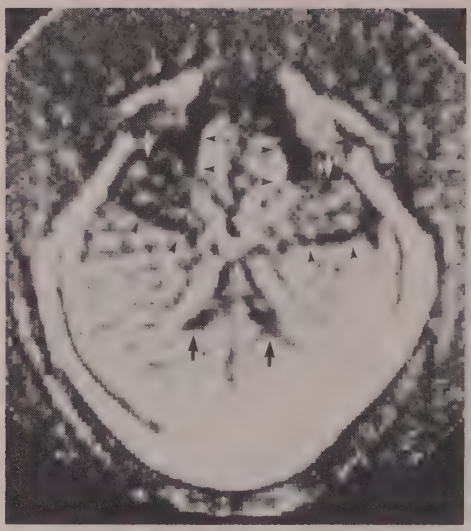

Figure 29. Nuclear magnetic resonance (NMR) (Courtesy EMI Medical Inc., Hayes, Middlesex, England). NMR scan of the head, with anterior to the top, demonstrates the orbits (arrowheads), globes (white arrows), ventricles (black arrows), calvarium and brain. Although still primitive, NMR does depict cross-sectional anatomy without exposing the patient to any ionizing radiation.

If the nuclei imaged are protons, regions with a high density of mobile protons produce white areas on the NMR image. The bone marrow in the diploic spaces, the fat in the orbit, and some mucous membranes such as that of the palate give a strong NMR signal and thus appear white on the NMR image. Regions with a low density of mobile protons such as cortical bone, teeth and air-filled spaces give a very low signal and appear dark on the NMR image (Fig. 29). Muscle and nervous tissue yield signals of intermediate strength and appear gray.

Thus far, NMR imaging has been utilized to produce cross-sectional images of the human wrist in vivo,[26, 28] and cross-sectional images of rabbit head cadavers.[27] It is known that edema and ischemia influence the NMR responses. It is felt, therefore, that NMR has great potential for depicting pathology in vivo.

SUMMARY

Attempts to address "advances" in diagnosis face the inherent risk of including information which only *seems* to be reliable. Current efforts must be based on limited data which will no doubt be reinterpreted after more extensive investigation. We have tried to minimize this risk by selecting our examples. If some interpretations ultimately prove invalid, then we can only hope you share our affection for the fluidity of concept and the changing nature of "fact" at the frontier.

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REFERENCES

1. Anderson, R. E.: Direct sagittal computed tomography scanning of the skull and its contents. Neuroradiology, *16*:603–604, 1978.
2. Bentson, J., Reza, M., Winter, J., et al.: Steroids and apparent cerebral atrophy on computed tomography scans. J. Comput. Assist. Tomog., 2:16–23, 1978.
3. Bergstrom, M., Ericson, K., Levander, B., et al.: Computed tomography of cranial subdural and epidural hematomas: Variation of attenuation related to time and clinical events such as rebleeding. J. Comput. Assist. Tomog., *1*:449–455, 1977.
4. Brownell, G. L., and Cochavi, S.: Transverse section imaging with carbon-11 labeled carbon monoxide. J. Comput. Assist. Tomog., 2:533–538, 1978.
5. Campbell, J. K., Houser, O. W., Stevens, J. C., et al.: Computed tomography and radionuclide imaging in the evaluation of ischemic stroke. Radiology, *126*:695–702, 1978.
6. Coin, G., Keranen, V. J., Pennink, M., et al.: Computerized tomography of the spine and its contents. Neuroradiology, *16*:271–272, 1978.
7. Drayer, B. P., and Rosenbaum, A. E.: Pediatric metrizamide CT cisternography: Cerebrospinal fluid circulation and hydrocephalus. Neurology, *28*:71–77, January 1978.
8. Drayer, B. P., Rosenbaum, A. E., and Higman, H. B.: Cerebrospinal fluid imaging using serial metrizamide CT cisternography. Neuroradiology, *13*:7–17, 1977.
9. Drayer, B. P., Rosenbaum, A. E., Reigel, D. B., et al.: Metrizamide computed tomography cisternography: Pediatric applications. Radiology, *124*:349–357, August 1977.
10. Drayer, B. P., Wilkins, R. H., Boehnke, M., et al.: Cerebrospinal fluid rhinorrhea demonstrated by metrizamide CT cisternography. Amer. J. Roentgenl., *129*:149–151, 1977.
11. Drayer, B. P., Wolfson, S. K., Boehnke, M., et al.: Physiologic changes in regional cerebral blood flow defined by xenon-enhanced CT scanning. Neuroradiology, *16*:220–223, 1978.
12. Dublin, A. B., and Dublin, W. B.: Cerebral pseudoatrophy and computed tomography: Two illustrative case reports. Surg. Neurol., *10*:209—212 (Sept.) 1978.
13. Enzmann, D. R., and Lane, B.: Cranial computed tomography findings in anorexia nervosa. J. Comput. Assist. Tomog., *1*:410–414, 1977.
14. Enzmann, D. R., and Lane, B.: Enlargement of subarachnoid spaces and lateral ventricles in pediatric patients undergoing chemotherapy. J. Pediatr., *92*:535–539, 1978.
15. Enzmann, D. R., Norman, D., et al.: Computed tomography of granulomatous basal arachnoiditis. Radiology, *120*:341–344, 1976.
16. Enzmann, D. R., Krikorian, J., Yorke, C., et al.: Computed tomography in leptomeningeal spread of tumor. J. Comput. Assist. Tomog., 2:448–455, 1978.
17. Felson, B.: Computerized Cranial Tomography. New York, Grune and Stratton, 1977.
18. Gado, M., Hanaway, J., and Frank, R.: Functional anatomy of the cerebral cortex by computed tomography. J. Comput. Assist. Tomogr., *3*:19, 1979.
19. Gallagher, T. J.: Easy coronal scans. Amer. J. Roentgen., *131*:535, 1978.
20. Gonzalez, C. F.: Grossman, C. B., and Palacios, E.: Computed Brain and Orbital Tomography. Technique and Interpretation. New York, John Wiley & Sons, 1976.
21. Hammerschlag, S. B., Wolpert, S. M., and Carter, B. L.: Computed coronal tomography. Radiology, *120*:219–220, July 1976.
22. Harwood-Nash, D. C., Fitz, C. R., Resjo, M., et al.: Computed tomographic metrizamide myelography of congenital abnormalities of the spinal canal and its contents in infants and children. Presented at the 16th Annual Meeting of The American Society of Neuroradiology, New Orleans, Feb. 26–March 2, 1978.
23. Hayward, R. W., Naeser, M. A., and Zatz, L. M.: Cranial computed tomography in aphasia. Radiology, *123*:653–660, June 1977.
24. Heinz, E. R., Martinez, J., and Haenggeli, A.: Reversibility of cerebral atrophy in anorexia nervosa and Cushing's syndrome. J. Comput. Assist. Tomog., *1*:415–418, 1977.
25. Hesselink, J. R., New, P. F. J., Davis, K. R., et al.: Computed tomography of the paranasal sinuses and face: Part II. Pathological anatomy. J. Comput. Assist. Tomog., 2:568–576, 1978.
26. Hinshaw, W. S., Andrew, E. R., Bottomley, P. A., et al.: Internal structure mapping by nuclear magnetic resonance. Neuroradiology, *16*:607–609, 1978.
27. Hinshaw, W. S., Andrew, E. R., Inst, F., et al.: Display of cross sectional anatomy by nuclear magnetic resonance imaging. Brit. J. Radiol., *51*:273–280, 1978.
28. Hinshaw, W. S., Bottomley, P. A., and Holland, G. N.: Radiographic thin-section image of the human wrist by nuclear magnetic resonance. Nature, 270:722–723, 1977.
29. Jacobson, R. E., Gargano, F. P., and Rosomoff, H. L.: Transverse axial tomography of the spine. Parts 1 and 2. J. Neurosurg., *42*:406–419, 1975.

30. James, A. E.: Cerebrospinal fluid imaging (cisternography). *In* Gottschalk, A., and Potchen, E. J., eds.: Diagnostic Nuclear Medicine. Baltimore, Williams and Wilkins, 1976, pp. 303–331.
31. Kasdon, D. L., Scott, R. M., Adelman, L. S., et al.: Cerebellar hemorrhage with decreased absorption values on computed tomography: A case report. Neuroradiology, *13*:265–266, 1977.
32. Kelcz, F., Hilal, S. K., Hartwell, P., et al.: Computed tomographic measurement of the xenon brain-blood partition coefficient and implications for regional cerebral blood flow: A preliminary report. Radiology, *127*:385–392, 1978.
33. Kido, D. K., Gould, R., Taati, F., et al.: Comparative sensitivity of CT scans, radiographs and radionuclide bone scans in detecting metastatic calvarial lesions. Radiology, *128*:371–375, 1978.
34. Kingsley, D., and Kendall, B. E.: Dependent layering of contrast medium in cystic astrocytomas. Neuroradiology, *14*:107–110, 1977.
35. Kinkel, W. R., and Jacobs, L.: Computerized axial transverse tomography in cerebrovascular disease. Neurology, *26*:924–930, 1976.
36. Kramer, R. A., and Janetos, G. P.: Image manipulation in the detection of bone lesions with CT scanning. Amer. J. Roentgen., *127*:593–594, 1976.
37. Laster, D. W., Moody, D. M., and Ball, M. R.: Resolving intracerebral hematoma: Alteration of the "ring sign" with steroids. Amer. J. Roentgen., *130*:935–939, 1978.
38. Latchaw, R. E., Gold, L. H. A., Moore, J. S., Jr., et al.: The nonspecificity of absorption coefficients in the differentiation of solid tumors and cystic lesions. Radiology, *125*:141–144, 1977.
39. Latchaw, R. E., Gold, L. H. A., and Tourje, E. J.: A protocol for the use of contrast enhancement in cranial computed tomography. Radiology, *126*:681–687, 1978.
40. Manelfe, C., Starling-Jardim, D., Touibi, S., et al.: Transsphenoidal encephalocele associated with agenesis of corpus callosum: Value of metrizamide computed cisternography. J. Comput. Assist. Tomog., 2:356–361, 1978.
41. Maravilla, K. R.: Computer reconstructed sagittal and coronal computed tomography head scans: Clinical applications. J. Comput. Assist. Tomog., 2:189–198, 1978.
42. Maroon, J. C., Bank, W. O., Drayer, B. P., et al.: Intracranial biopsy assisted by computerized tomography. J. Neurosurg., *46*:740–744, 1977.
43. Messina, A. V., Potts, D. G., Rottenberg, D., et. al.: Computed tomography: Demonstration of contrast medium within cystic tumors. Radiology, *120*:345–347, 1976.
44. Mikhael, M. A.: Radiation necrosis of the brain: Correlation between computed tomography, pathology and dose distribution. J. Comput. Assist. Tomog., 2:71–80, 1978.
45. Mohr, J. P., Pessin, M. S., Finkelstein, S., et al.: Broca aphasia: Pathologic and clinical. Neurology, *28*:311–324, 1978.
46. Momose, K. J., Kjellberg, R. N., and Kliman, B.: High incidence of cortical atrophy of the cerebral and cerebellar hemispheres in Cushing's disease. Radiology, *99*:341–348, 1971.
47. Moran, C. J., Naidich, T. P., Gado, M. H., et al.: Leptomeningeal findings in computerized tomography (CT) of subarachnoid hemorrhage. J. Comput. Assist. Tomog., 2:520–521, 1978.
48. Moran, C. J., Naidich, T. P., Gado, M. H., et al.: Central nervous system lesions biopsied and treated by CT-guided needle placement. Radiology, *131*:681–686, 1979.
49. Naeser, M. A., and Hayward, R. W.: Lesion localization in aphasia with cranial computed tomography and the Boston Diagnostic Aphasia Exam. Neurology, 28:545–551, 1978.
50. Naidich, T. P., Lin, J. P., Kricheff, I. I., et al.: Computerized axial tomography in the diagnosis of extra-axial posterior fossa masses. Radiology, *120*:333–339, 1976.
51. Naidich, T. P., Pinto, R. S., Kushner, M. J., et al.: Evaluation of sellar and parasellar masses by computerized axial tomography. Radiology, *120*:91–99, 1976.
52. Naidich, T. P., Pudlowski, R. M., Leeds, N. E., et al.: Hypoglossal palsy: Computed tomography demonstration of denervation hemiatrophy of the tongue associated with glomus jugulare tumor. J. Comput. Assist. Tomogr., 2:630–632, 1978.
53. Naidich, T. P., Pudlowski, R. M., Moran, C. J., et al.: Computed tomography of spinal fractures. Advances in Neurology, 22:207–253, 1979. New York, Raven Press.
54. New, P. F. J., and Aranow, S.: Attenuation measurements of whole blood and blood fractions in computed tomography. Radiology, *121*:635–640, 1976.
55. New, P. F. J., and Scott, W. R.: Computed Tomography of the Brain and Orbit (EMI Scanning). Baltimore, Maryland, Williams & Wilkins, 1975.
56. Norman, D., Enzmann, D. R., and Newton, T. H.: Otpimal contrast dosage in cranial computed tomography. Amer. J. Roentgen., *131*:687–689, 1978.
57. Norman, D., Price, D., Boyd, D., et al.: Quantitative aspects of computed tomography of the blood and cerebrospinal fluid. Radiology, *123*:335–338, 1977.
58. O'Doherty, D. S., Schellinger, D., and Raptopoulos, V.: Computed tomographic patterns of pseudohypertrophic muscular dystrophy: Preliminary Results. J. Comput. Assist. Tomog., *1*:482–486, 1977.

59. Orrison, W. W., Robertson, W. C., and Sackett, J. F.: Computerized tomography in chronic subdural hematomas (effusions) of infancy. Neuroradiology, *16*:79–81, 1978.
60. Ostertag, C. B., and Mundinger, F.: Diagnosis of normal-pressure hydrocephalus using CT with CSF enhancement. Neuroradiology, *16*:216–219, 1978.
61. Partain, C. L., Scatliff, J. H., Staab, E. V., et. al.: Quantitative multiregional CSF kinetics using serial, metrizamide enhanced computed tomography. J. Comput. Assist. Tomog., 2:467–470, 1978.
62. Peterson, H. O., and Kieffer, S. A.: Introduction to Neuroradiology. Hagerstown, Maryland, Harper & Row, 1972.
63. Pollack, J. A.: Stroke. *In* Norman, D., Korobkin, M., and Newton, T. H., eds.: Computed Tomography, University of California, Los Angeles, 1977, pp. 255–262.
64. Radue, E. W., and Kendall, B. E.: Iodide and xenon enhancement of computed tomography (CT) in multiple sclerosis (MS). Neuroradiology, *15*:153–158, 1978.
65. Radue, E. W., and Kendall, B. E.: Xenon enhancement in tumours and infarcts. Neuroradiology, *16*:224–227, 1978.
66. Raichle, M. E.: Quantitative in vivo autoradiology with positron emission tomography. Brain Res., in press.
67. Rosenbaum, A. E., Drayer, B. P., Dubois, P. J., et al.: Visualization of small extracanalicular neurilemomas. Arch. Otolaryngol., *104*:239–343, May 1978.
68. Rosenblum, M. L., Hoff, J. T., Norman, D., et al.: Decreased mortality from brain abscesses since advent of computerized tomography. J. Neurosurg, *49*:658–668, 1978.
69. Rottenberg, D. A., Deck, M. D. F., Allen, J. C.: Metrizamide washout as a measure of CSF bulk flow. Neuroradiology, *16*:203–206, 1978.
70. Salar, G., Carteri, A., and Zampieri, P.: The diagnosis of CSF fistulas with rhinorrhea by isotope cisternography. Neuroradiology, *15*:185–187, 1978.
71. Scotti, G., Ethier, R., Melancon, D., et al.: Computed tomography in the evaluation of intracranial aneurysms and subarachnoid hemorrage. Radiology, *123*:85–90, 1977.
72. Stephanov, S.: Experience with multiloculated brain abscesses. J. Neurosurg., *49*:199–203, 1978.
73. Takahashi, M., Arii, H., and Tamakawa, Y.: Comparison of metrizamide CT cisternography with radionuclide cisternography in abnormal cerebrospinal fluid dynamics. Neuroradiology, *16*:199–202, 1978.
74. Tamaki, N., Kanazawa, Y., Asada, M., et al.: Comparison of cerebrospinal fluid dynamics studied by computed tomography (CT) and radioisotope (RI) cisternography. Neuroradiology, *16*:193–198, 1978.
75. Ter-Pogossan, M. M., Mullani, N. A., Hood, J., et al.: A multislice positron emission computed tomography (PETT IV) yielding transverse and longitudinal images. Radiology, *128*:477–484, 1978.
76. Wing, S. D., Norman, D., Pollock, J. A., et al.: Contrast enhancement of cerebral infarcts in computed tomography. Radiology, *121*:89–92, 1976.
77. Wolf, B. S., Nakagawa, H., and Staulcup, P. H.: Feasibility of coronal views in computed scanning of the head. Radiology, *120*:217–218. 1976.
78. Yamamoto, Y. L., Thompson, C. J., Meyer, C., et al.: Dynamic positron emission tomography for study of cerebral hemodynamics in a cross section of the head using positron-emitting ^{68}Ga-EDTA and ^{77}Kr. J. Comput. Assist. Tomog., *1*:43–56, 1977.
79. Yock, D. H., Jr., and Marshall, W. H., Jr.: Recent ischemic brain infarcts at computed tomography: Appearances pre- and postcontrast infusion. Radiology, *117*:599–608, 1975.
80. Zilkha, E., Kendall, B. E., Loh, L., et al.: Diagnosis of subdural haematoma by computed axial tomography: Use of xenon inhalation for contrast enhancement. Neurology, *41*:370–373, 1978.
81. Zimmerman, R. A., Patel, S., Bilaniuk, L. T.: Demonstration of purulent bacterial intracranial infections by computed tomography. Amer. J. Roentgen. *127*:155–165, 1976.
82. Zimmerman, R. D., Leeds, N. E., and Naidich, T. P.: Ring blush associated with intracerebral hematoma. Radiology, *122*:707–711, 1977.

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Anticoagulant Treatment to Prevent Cerebral Infarction

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The decision to use emergency or semi long-term anticoagulant treatment to prevent cerebral infarction is made only after careful analysis of each patient and evaluation of the relative priority of other treatments, i.e., surgical (thrombendarterectomy), antipolycythemia, correction of defective cardiac output, anticerebral edema, and so forth.

Anticoagulant treatment (heparin or warfarin) is potentially dangerous. This is also true of many standard therapies, i.e., insulin, digitalis, and steroids. If anticoagulant treatment is used, certain guidelines should be followed: (1) Indications for anticoagulant therapy must be precisely defined after work-up[31] of the patient. (2) The physician must have appropriate knowledge concerning the clinical pharmacology of the drug. (3) Accurate tests of prothrombin time (PT) and/or partial thromboplastin time (PTT) must be available. (4) The patient must comply (100 per cent) with instructions. (5) Contraindications must be assessed: (a) bleeding or potential bleeding lesions are a contraindication; (b) high blood pressure must be controlled within a few days after anticoagulant treatment is started.

PREVENTION OF EMBOLIZATION FROM CARDIAC SOURCES

Prevention of recurrent embolization from a cardiac source is the most important indication for *long term* anticoagulant treatment.

Prosthetic Cardiac Valves

The usual treatment for prevention of cerebral emboli (or emboli to other portions of the body) from prosthetic heart valves has been the administration of oral anticoagulants. Duvoisin et al.[9] studied the risk of thromboembolism after insertion of prosthetic valves by constructing actuarial curves showing a proportion of patients with embolism at

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increasing time intervals postoperatively. This study suggests that the risk of thromboembolism diminishes with time, particularly by the third postoperative year. The risk of fatality averaged 15 per cent; none of the nonfatal embolisms resulted in significant continuing disability, save for 7 per cent of the cerebral embolisms. Anticoagulants exerted a beneficial effect on patients having replacement of the aortic valve with a ball-valve prosthesis, particularly when anticoagulant therapy was carefully controlled. The use of anticoagulants continues to be the common recommendation except for monograph replacement valves where postoperative embolism is not as significant a problem as our prosthetic cardiac valves. Sullivan et al.[38] have reported that only one patient of 42 (553 months follow-up) had two embolic events while receiving dipyridimole and anticoagulants, whereas 9 of 50 patients (695 months follow-up) had 17 embolic events while receiving anticoagulant and a placebo.

Rheumatic Heart Disease with Mitral Stenosis

Rheumatic heart disease with mitral stenosis (with or without atrial fibrillation) has long been associated with embolic events to various organs, often the brain. Oral anticoagulant therapy has been established as the preventive treatment of choice.[1, 14, 22, 35, 39, 49] Treatment is generally started after the first embolic event (wherever the site of the embolus). Carter[7] found that the recurrence rate after this type of embolism is about 50 per cent the first year and that this incidence can be significantly reduced in the first 6 months by using anticoagulant therapy. He noted that if rheumatic atrial fibrillation is the source of cerebral embolism, the anticoagulant treatment must be continued indefinitely unless sinus rhythm is restored. If the initial embolic episode is to a site other than brain, anticoagulant treatment should be started immediately. If the embolic event is to brain, I start intravenous heparin immediately if the neurologic defect is minimal (i.e., normal consciousness and mild hemiparesis).[44] However, if the neurologic defect is severe (i.e., hemiplegia with or without decreased consciousness) I wait 3 to 5 days before beginning anticoagulant therapy. In the latter instance the embolic infarct is very hemorrhagic and may be made worse by immediate action.[44]

Atrial Fibrillation

Atrial fibrillation has been recognized as a strong risk factor for stroke. In many instances the cause of the atrial fibrillation is nonvalvular heart disease.[12] When there is an embolic event in the presence of atrial fibrillation, long-term anticoagulant treatment is indicated[2, 8] (the usual precautions must be observed).

TRANSIENT ISCHEMIC ATTACKS

Transient ischemic attack should be defined precisely. (See References 31 for details of standard definition of transient ischemic attacks.)

Transient ischemic attacks are divided into those consisting of phenomena characteristic of ischemia in the vertebrobasilar system and of ischemia in the carotid system. The latter are more frequent and surgery is often selected as the treatment of choice (practical availability of the cervical portion of the internal carotid artery).

Transient ischemic attacks are the most important warning that cerebral infarction may occur. Since the initial reports[33, 34] in 1955 there have been numerous confirmatory observations.[4, 5, 13, 15, 25, 37] A cluster of recent transient ischemic attacks is a particularly serious warning that cerebral infarction may happen.[29] The first month (after a transient ischemic attack) is the most dangerous time;[27, 43] 50 per cent of those who have a stroke after a transient ischemic attack will have the stroke in one year and after the onset of transient ischemic attack the stroke occurrence rate is about 5 per cent per year. The latter is about 5 times the expected rate for a population with a similar distribution. By inference a transient ischemic attack 4 to 5 years before a specific point in time is a very weak predictor for stroke.

Carotid System

If the transient ischemic attack, or particularly a cluster of transient ischemic attacks, has occurred within the preceding 30 days the patient is hospitalized and continuous heparin infusion (heparin pump) is started, presuming no contraindication is present. The PTT is maintained at about 2 times the normal while work-up of the patient goes on. The mechanism of transient ischemic attacks varies; treatment must attempt to correct the abnormal mechanism. (For full discussion see reference 32). In most instances angiography-surgery is advised. The morbidity-mortality rate for the combination of angiography-surgery should probably not exceed 3 per cent (TIA patients). If no surgically accessible lesion is present, oral anticoagulant is used, presuming the guidelines are followed. I continue the oral anticoagulant for about 6 months; the PT is kept at 2 times or slightly less than 2 times the normal value. (For details concerning results see reference 32).

Vertebral Basilar System

The same *work-up treatment* plan is used as for carotid transient ischemic attack, except angiography is unlikely to display an operable lesion. In instances where there is uncertainty about whether the transient ischemic attacks are caused by pathology in the carotid system or vertebral basilar system, angiography probably should be done.

PROGRESSING STROKE (STROKE IN EVOLUTION)

A progressing stroke or stroke-in-evolution is that temporal category in which there has been progression (increased severity of the neurologic signs) within recent minutes — this value judgment may be made from the analysis of the history or by repeated examination of the patient. It may be difficult to be certain from minute to minute, or

even from hour to hour, whether further progression will occur. However, if the neurological deficit has worsened in the few minutes prior to making a judgment about a particular patient's status, the situation should be categorized as a progressing cerebral infarction or stroke-in-evolution. If the site of the lesion is the carotid system, 18 to 24 hours of observation, without progression, is ordinarily sufficient time to mean that further progression is unlikely and that the patient's temporal profile status should no longer be characterized as "progressing stroke" (now should be called completed stroke). If the lesion is in the territory supplied by the vertebral basilar system, a longer period of time (up to 72 hours) should probably elapse before the patient is removed from the progressing stroke category and is designated as a "completed stroke," since there is a tendency for periods of progression to be separated by many hours when the impaired circulation is in the vertebral basilar system.

The extraordinary variability in the natural history of acute progressing stroke makes it important that comparison be made of treated and untreated patients of similar type. An example of this variability was reported in 1955.[27] Two hundred and four consecutive patients with acute onset of progressing stroke in the carotid system were observed. At 14 days after onset, 12 per cent of the patients were normal, 5 per cent (using motor phenomena as a basis for comparison) had varying degrees of monoparesis, 69 per cent had varying degrees of hemiparesis, and 14 per cent were dead. In most instances in the literature, little distinction is made between progressing stroke in the territory of the vertebral basilar system and progressing stroke in the carotid system. With anticoagulant treatment, it was reported[28] that 8.5 per cent of patients with acute progressing vertebral basilar thrombosis died, whereas 58.9 per cent of a similar untreated group died. It is also necessary, in studies of comparisons of treatment, to include only patients who have had the onset of trouble in the preceding few hours. If subjects are studied with an onset of neurologic focal trouble 48 or 72 hours prior to admission, the "progressing stroke" category will include many patients in whom the dynamic physiological progress has reached its maximum degree, and from that point in time forward, the natural history of such patients is usually one of improvement, sometimes at a fairly rapid rate. Inclusion of this type of patient in a test of effectiveness of a treatment must produce a false result in favor of the treatment. As observed in a report[21] in 1976, 96 per cent of patients, who have stopped progressing, will have some improvement.

In the patient with acute progressing stroke (either system) there may be uncertainty about whether intracerebral bleeding is present or not. The experienced clinician can answer this question with satisfactory accuracy; however, the CT head scan is close to 100 per cent accurate and should be done as part of the initial evaluation. If no evidence of bleeding is seen an intravenous infusion (heparin pump) of heparin is started. If the patient is hemiplegic and/or has a decreased level of consciousness I assume that maximum ischemia is present (progression of focal ischemia per se is unlikely) and I do not start

heparin or give anticoagulant. The decision about treating with antiedema agents is purposely not discussed in this paper. Five reports compare patients treated and untreated with anticoagulants in reference to progression.[4, 6, 11, 13, 28] All of these studies demonstrate protection by anticoagulants in acute progressing stroke. In discussing treatment of acute progressing stroke, it is now usual for the experienced clinician[24, 36, 41] to advise emergent anticoagulant therapy in the circumstances described above. In searching the literature it is sometimes difficult to find a description of anticoagulant treatment — it may not be in the title of the paper. An example is a recent manuscript[18] from Massachusetts General Hospital concerning "Symptomatic Middle Cerebral Artery Stenosis" in 16 patients. The authors wrote, "Our preliminary conclusions suggest that medical therapy, including anticoagulants, should be initiated early, before the occurrence of complete occlusion." Oral anticoagulant therapy is started as soon as feasible — it is continued for 2 to 3 months. The danger of intracerebral hemorrhage associated with anticoagulant treatment is greatly increased after 1 year of treatment.[37] Only one patient of 9 developing intracerebral hemorrhage while taking anticoagulants had been taking them for less than one year. The blood pressure, if elevated, must be controlled during treatment — and should continue to be controlled, as it constitutes a significant risk factor for stroke.

COMPLETED STROKE

Completed stroke refers to the instance in which the focal neurologic deficit is stable; the number of hours of stability suggested for making this decision is probably 24 to 48 in the carotid system and 72 to 96 hours in the vertebral basilar system. It is obvious that the dynamic pathophysiology is different in an instance where "completion" has been present for only 2 to 3 days in comparison to a situation where the stroke was "completed" many weeks or months before the time of evaluation. The work "completed" does not imply that a particular neurologic sign has become maximum in quantity, i.e., hemiplegia as distinguished from hemiparesis. A cerebral infarct may be judged to be completed when the neurological deficit is minor or also when the neurological deficit is very severe (when the prolonged neurological deficit has a duration more than 24 hours but less than 3 weeks, the term "reversible ischemic neurological deficit" or RIND is sometimes used).

As in patients with transient ischemic attack or progressing stroke, the plan for treating a patient with a "completed stroke" is designed after appropriate work-up has been completed. The objective is to prevent another stroke! Cardiac defects should be corrected, high blood pressure controlled, polycythemia treated, and in some instances angiography would be indicated in the search for surgically correctable pathogenetic lesions.

In this context (completed stroke) the role of anticoagulant treat-

ment is limited. Three[10, 20, 23] of nine papers[3, 4, 10, 17, 19, 20, 23, 26, 40] show percentages of protection against subsequent stroke slightly in favor of treatment. This statement does not take into account the complications which occur. The other reports showed no benefit or actual danger. In one study[4] the treated patients had a 10 per cent incidence of severe hemorrhage. On the basis of such a complication rate it would appear that anticoagulant treatment is actually contraindicated. Another study[17] demonstrated a similar result. More favorable was a report[23] that 22 per cent of untreated patients had recurrent cerebral infarction; only 1 per cent of those receiving anticoagulants had such lesions. Seven per cent of those treated had hemorrhages. On balance the record is against long-term anticoagulant treatment of completed stroke. With careful management the danger of anticoagulant treatment is much less in the first few months after a stroke — perhaps 4 to 6 months of anticoagulant therapy would be wise — but no data bolster this notion.

SUMMARY

The indications for anticoagulant treatment to prevent cerebral infarction or progression of cerebral infarction are now clear. The indications are: (1) Prevention of recurrent embolization from a cardiac source (long-term anticoagulant treatment). (2) Transient ischemic attacks (particularly vertebrobasilar system) if a surgically accessible causative lesion, polycythemia, and thrombocytosis are not present (anticoagulants for a few months.) (3) Progressing stroke in either system assuming that the neurological defect is partial and CT scan shows no evidence of bleeding (anticoagulants for a few months.) (4) Rarely, completed stroke (long term).

REFERENCES

1. Adams, G. F., Merrett, J. D., Hutchinson, W. M., et al.: Cerebral embolism and mitral stenosis: Survival with and without anticoagulants. J. Neurol. Neurosurg. Psychiat., *37*:378–383, 1974.
2. Askey, J. M., and Cherry, C. B.: Thromboembolism associated with auricular fibrillation. J.A.M.A., *144*:97–100, 1950.
3. Baker, R. N.: An evaluation of anticoagulant therapy in the treatment of cerebrovascular disease: Report of the Veterans Administration Study of Atherosclerosis. Neurology, *11*:132–138, 1961.
4. Baker, R. N., Browart, J. A., Fang, H. C., et al.: Anticoagulant therapy in cerebral infarction. Neurology (Minneap.), *12*:823–835, 1962.
5. Baker, R. N., Schwartz, W., and Rose, A. S.: Transient ischemic attacks—a report of a study of anticoagulant treatment. Neurology (Minneap.), *16*:841–847, 1966.
6. Carter, A. B.: Anticoagulant treatment in progressing stroke. Brit. Med. J., 2:70–73, 1961.
7. Carter, A. B.: Strokes. Natural history and progression. Proc. Roy. Soc. Med., 56:483–486, 1963.
8. Cosgriff: Prophylaxis of recurrent embolism of intracardiac origin. J.A.M.A., *143*:870–872, 1950.
9. Duvoisin, G. E., Brandenburg, R. O., and McGoon, D. G.: Factors affecting thromboembolism associated with prosthetic heart valves. Circulation (Suppl. I), *35*:170–176, 1967.

10. Enger, E., and Boysen, S.: Long-term anticoagulant therapy in patients with cerebral infarction. A controlled clinical study. Acta Med. Scand., *178* (Suppl. 438): 1–61, 1965.
11. Fisher, C. M.: Anticoagulant therapy in cerebral thrombosis and cerebral embolism. A national cooperative study, interium report. Neurology (Minneap.), *11*:119–131, 1961.
12. Fisher, C. M.: Stroke with atrial fibrillation. Stroke, *9*:96, 1978.
13. Fisher, C. M.: Use of anticoagulants in cerebral thrombosis. Neurology (Minneap.), *8*:311–332, 1958.
14. Fleming, H. A., and Bailey, S. M.: Mitral valve disease, systemic embolism and anticoagulant. Postgrad. Med. J., *47*:599–604, 1971.
15. Friedman, G. D., Wilson, S., Mosier, J. M., et al.: Transient ischemic attacks in a community. J.A.M.A., *210*:1428–1431, 1969.
16. Furlan, A. J., Whisnant, J. P., and Iveback, L. R.: The decreasing incidence of primary intracerebral hemorrhage: A population study. Ann. Neurol., *5*:167–373, 1979.
17. Hill, A. B., Marshall, J., and Shaw, D. A.: Cerebrovascular disease: Trial of long-term anticoagulant therapy. Brit. Med., J., *2*:1003–1006, 1962.
18. Hinton, R. C., Mohr, J. P., Ackerman, R. H., et al.: Symptomatic middle cerebral artery stenosis. Ann. Neurol., *5*:152–157, 1979.
19. Howard, F. A., Cohen, P., Hickler, R. B., et al.: Survival following stroke. J.A.M.A., *183*: 921–925, 1963.
20. Howell, D. A., Tatlow, S. F. T., and Feldman, S.: Observation on anticoagulant therapy in thromboembolic disease of the brain. Can. Med. Assoc. J., *90*:611–614, 1964.
21. Jones, H. R., Jr., and Millikan, C. H.: Temporal profile of acute cerebral infarction in the distribution of the internal carotid artery. Stroke, *7*:64–71, 1976.
22. McDevitt, E.: Treatment of cerebral embolism. Mod. Treat., *2*:52–63, 1965.
23. McDowell, F., and McDevitt, E.: Treatment of the completed stroke with long-term anticoagulant: Six and one half years experience. *In*: Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebral Vascular Diseases. 4th Princeton Conference. New York, Grune and Stratton, 1965, pp. 185–199.
24. Marshall, J.: The Management of Cerebral Vascular Disease. London, Blackwell Scientific Publications, 3rd ed., 1976, pp. 176–178.
25. Marshall, J.: *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebrovascular Diseases. 4th Princeton Conference. New York, Grune and Stratton, 1965, p. 194.
26. Marshall, J., and Shaw, D. A.: Anticoagulant therapy in acute cerebrovascular accidents. A controlled trial. Lancet, *1*:995–998, 1960.
27. Matsumoto, N., Whisnant, J. P., Kurland, L. T., and et al.: Natural history of stroke in Rochester, Minnesota, 1955–1969: An extension of a previous study, 1945–1954. Stroke, *4*:20–29, 1973.
28. Millikan, C. H.: Anticoagulant therapy in cerebrovascular disease. *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebrovascular Diseases. 4th Princeton Conference. New York, Grune and Stratton, 1965, p. 183.
29. Millikan, C. H.: Discussion. *In* McDowell, F. H., and Brennan, R. W., eds.: Cerebrovascular Diseases. 8th Princeton Conference. New York, Grune and Stratton, 1973, p. 23.
30. Millikan, C. H.: Evaluation of carbon dioxide inhalation for acute focal cerebral infarction. Arch. Neurol., *73*:324–328, 1955.
31. Millikan, C. H., Bauer, R., et al.: Classification and outline of cerebrovascular disease. II. Stroke, *6*:594–612, 1975.
32. Millikan, C. H., and McDowell, F. H.: Treatment of transient ischemic attacks. Stroke, *9*:299–308, 1978.
33. Millikan, C. H., and Siekert, R. G.: Studies in cerebrovascular disease I. The syndrome of intermittent insufficiency of the basilar arterial system. Proc. Staff Meet. Mayo Clin., *30*:61–68, 1955.
34. Millikan, C. H., and Siekert, R. G.: Studies in cerebrovascular disease. IV. The syndrome of intermittent insufficiency of the carotid arterial system. Proc. Staff Meet. Mayo Clinic, *30*:186–191, 1955.
35. Owren, P. A.: The results of anticoagulant therapy in Norway. Arch. Intern. Med., *111*: 240–247, 1963.
36. Scheinberg, P.: Modern Practical Neurology. New York, Raven Press, 1977.
37. Siekert, R. G., Whisnant, J. P., and Millikan, C. H.: Surgical and anticoagulant therapy of occlusive cerebrovascular disease. Ann. Intern. Med., *58*:637–641, 1963.
38. Sullivan, J. M., Harken, D. E., and Gorlin, R.: Affect of dipyridamole on the incidence of arterial emboli after cardiac valve replacement. Circulation (Suppl. I), *39*:I-149, I-153, 1969.
39. Szekely, P.: Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. Brit. Med. J., *1*:1209–1212, 1964.
40. Thygesen, P., Christensen, E., and Dyrbye, M., et al.: Cerebral apoplexy: A clinical, radiological, electroencephalographic and pathological study with special reference to the prognosis of cerebral infarction and the result of long-term AC therapy. Dan. Med. Bull., *11*:233–257, 1964.

41. Toole, J. F.: Management of TIAs and acute cerebral infarction. *In* Thompson, R. A., and Green, J. R., eds.: Advances in Neurology, Vol. 16, New York, Raven Press, 1977, pp. 71–80.
42. Whisnant, J. P.: Discussion of progressing stroke: anticoagulant therapy. *In* Millikan, C. H., Siekert, R. G., and Whisnant, J. P., eds.: Cerebrovascular Diseases. 3rd Princeton Conference. New York, Grune and Stratton, 1961, pp. 156–157.
43. Whisnant, J. P., Matsumoto, N., and Elveback, L. R.: Transient cerebral ischemic attacks in a community: Rochester, Minnesota, 1955–1969. Mayo Clinic Proc., *48*:194–198, 1973.
44. Whisnant, J. P., Millikan, C. H., et al.: Effect of anticoagulants on experimental cerebral infarction. Clinical implications. Circulation, *20*:56–65, 1959.
45. Wright, I. S., and McDevitt, E.: Cerebrovascular Diseases: Their significance, diagnosis and present treatment, including the selective use of anticoagulant substances. Ann. Intern. Med., *41*:682–698, 1954.

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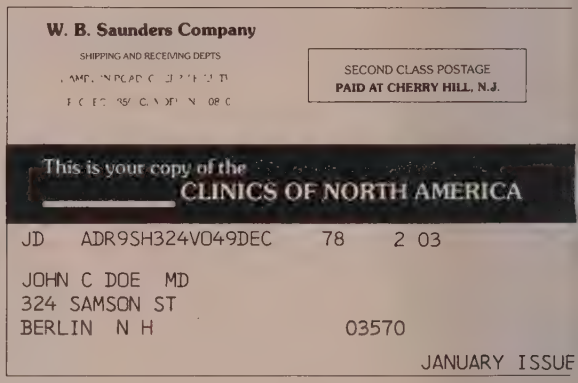

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